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EFFECT OF ACTH AND CORTISONE ON FAT ABSORPTION IN STEATORRHEA OF VARIOUS CAUSES*

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THE steatorrhea occurring in nontropical sprue or the "malabsorption syndrome" has been shown by several observers to be markedly decreased by treatment with ACTH or cortisone.[1-6] The purpose of this study was to determine whether fat absorption in steatorrhea other than that caused by nontropical sprue might be improved by steroid therapy. Furthermore, it was hoped that the data obtained might help determine whether the steroid administration had a specific beneficial effect on fat absorption by the intestinal mucosa.

Four patients with steatorrhea due to different mechanisms were studied. Case 1 had steatorrhea associated with a subtotal gastric resection and gastrojejunostomy; the basic defect causing steatorrhea in this condition is not clear, but both pancreatic function and intestinal absorption are apparently normal. Case 2 had extensive ileojejunitis and apparently had severe malabsorption secondary to this disease, so-called secondary sprue. Case 3 had pancreatic calcinosis with pancreatic insufficiency; in this disease a lack of fat-splitting enzyme presumably causes the impaired fat absorption. Case 4 had severe nontropical sprue, with malabsorption of many nutrient elements.

METHODS

The first 3 patients were hospitalized on the metabolic ward, the diets being weighed daily. During every other period a representative twenty-four-hour diet sample was analyzed for fat and nitrogen. All stools were collected in five-day pools, mixed, and quantitative fat determinations done by a modification of the method of van de Kamer et al.[7] Nitrogen was determined by the macro-Kjeldahl technic. The fat balance was determined during 2 to 4 preliminary control periods of five days each. ACTH and cortisone were then given for 9 to 20 periods of five days each. The dosage of cortisone varied from 50 to 250 mg. a day given intramuscularly. ACTH was given in doses of 40 to 200 mg. daily — also intramuscularly. The clinical course of each patient was carefully observed.

In addition to fat balance, nitrogen balance was determined in Cases 1 and 3. Laboratory tests to demonstrate the effects of ACTH and cortisone were done frequently. Thus, complete blood counts, including eosinophil counts, serum electrolytes, blood sugar and blood urea nitrogen were determined during every metabolic period.

Case 4 was studied on a general medical ward, the diet being calculated from food tables. During 3 periods lasting seven days each, at various stages of the disease, stool pools were collected, and quantitative fat determinations carried out.

RESULTS

The patient with steatorrhea due to subtotal gastrectomy (Case 1) showed no decrease of fecal fat during 2 periods of cortisone and 5 periods of ACTH. During two control periods he was in positive nitrogen balance. Cortisone did not affect this, but during ACTH administration negative balance developed, as was to be expected (Fig. 1).

The patient with intestinal malabsorption secondary to ileojejunitis (Case 2) showed a moderate decrease of steatorrhea, the level of fat decreasing from 50 per cent to approximately 25 per cent of the daily intake when he was given cortisone and ACTH. This decrease was concomitant with general clinical improvement (Table 1).

In the patient with pancreatic insufficiency (Case 3) there was some fluctuation in fecal fat excretion, but there was no consistent improvement and no evidence that cortisone influenced fat absorption. During 4 control periods he was in slightly positive nitro-

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gen balance, and with cortisone this became negative.

When he was given Tween-80 there was no effect on fat or nitrogen excretion. Later, during the administration of pancreatic extract there was a pronounced decrease in both total fat and nitrogen excretion, and the patient was in positive nitrogen balance (Fig. 2).

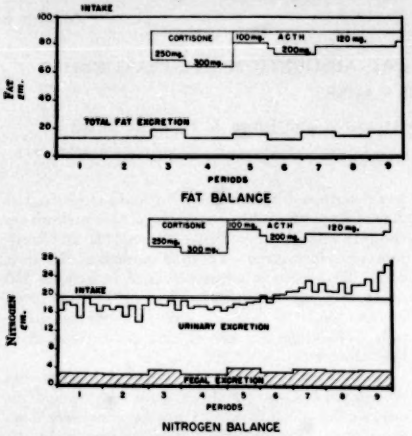


FIGURE 1. *Effect of Cortisone and ACTH on Fat and Nitrogen Balance in Case 1.*

The patient with nontropical sprue showed marked general clinical improvement and a reduction of fecal fat from 84 per cent to 25 per cent of daily intake when she was treated with cortisone (Table 2).

Case histories and detailed observations in the study of each patient are as follows:

Case Reports

CASE 1. B.R.S., a 56-year-old man, manifested symptoms of a duodenal ulcer in 1944, and in 1947, because of an episode of hematemesis, a subtotal gastrectomy and bilateral vagotomy were performed. During the following year the weight decreased from 155 to 114 pounds. He felt weak and exhausted and was able to eat only small meals, and in addition, because of unpleasant aftereffects, he avoided food rich in sugar and fat. After meals he felt hot and flushed and experienced epigastric distress, nausea and occasional vomiting. Since 1948 he had had diarrhea, with 5 to 8 light-colored, foamy stools daily.

Physical examination revealed a gaunt, pale man, 6 feet tall and weighing 117 pounds. The heart and lungs were not remarkable. The blood pressure was 110/80. The abdomen was not distended. The liver was normal in size.

The red-cell count was 3,800,000, the hematocrit 39 per cent, and the hemoglobin 12.8 gm. per 100 cc. The white-cell count was 7600, with a normal differential. Examination of the urine and an oral glucose tolerance test were negative. The serum calcium was 9.8 mg., and the inorganic phosphorus 3.6 mg. per 100 cc. Liver-function tests were negative. Gastric analysis showed low-normal amounts of free hydrochloric acid. Bone-marrow biopsy was negative. X-ray studies of the upper intestinal tract demonstrated a small remaining stomach segment, a functioning gastroenterostomy and a coarse mucosal pattern of the stomach and jejunum.

The results of the fat-balance study are shown in Fig. 1. The patient was given a measured diet containing 100 gm. of fat daily. Stools were collected for 5-day periods, and the fat content determined quantitatively for each period. During 2 control periods the fecal fat averaged 14 per cent of the ingested fat. He was then given cortisone, 250 mg. and 300 mg. for 1 period each. No significant changes in fat excretion occurred. After this he was given ACTH in doses of 100 to 200 mg. daily for 5 periods. The fecal fat excretion remained essentially the same. During the treatment periods he manifested the changes that normally accompany the administration of large doses of cortisone and ACTH. He became euphoric, and his appetite increased. He gained 9 pounds in weight as a result of water retention. The eosinophil count dropped, particularly when he was given ACTH; 11-oxysteroid excretion rose from 5.97 to 10.34 mg. per 24 hours when he was on ACTH. The stool fat averaged 15 per cent of intake and only once during the 7 treatment periods was the fecal fat slightly lower than that during the control periods.

TABLE 1. *Effect of Cortisone and ACTH on Fat Absorption in Case 2 As Measured by the Relation of Dietary and Fecal Fat.*

Period	Dietary Fat	Fecal Fat	Fecal Fat	Cortisone	ACTH
	gm./day	gm./day	% of intake	mg.	mg.
1	94.7	46.0	48	—	—
2	94.7	48.2	52	—	—
—*					
3	94.7	95.4	100	250	—
4	94.7	58.9	62	200	—
5	94.7	46.3	50	100	—
6	94.7	28.3	28	100	—
—†					
7	51.4	20.2	38	—	80
8	51.4	22.2	46	—	60
9	51.4	21.4	42	—	80
10	51.4	32.3	64	100	60
11	51.4	23.9	45	100	40
12	51.4	18.2	35	100	40
13	51.4	14.9	28	100	40
14	51.4	18.6	35	100	40
15	51.4	12.6	24	100	40
16	51.4	11.8	22	100	40
—‡					
17	90.0	16.4	18	50	—
18	90.0	12.3	25	50	—
19	90.0	24.7	27	50	—
20	90.0	20.4	23	50	—

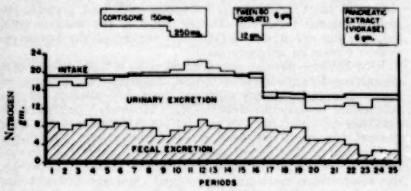
* 9-day interruption for operation.
† 16-day interruption for operation.
‡ 42-day interruption.

In this case neither cortisone nor ACTH had any beneficial effect on the steatorrhea resulting from a subtotal gastric resection (Fig. 1).

CASE 2. M.B.A., a 30-year-old man, noted abdominal distress, diarrhea and weight loss in 1941. He felt fairly

well until April, 1952, when severe symptoms recurred, necessitating hospitalization at the Los Angeles Veterans Administration Hospital in the following month. Physical examination on admission revealed a cachectic man who weighed 105 pounds, and whose temperature was 100°F. His skin, particularly the exposed surfaces, appeared abnormally tanned. The heart and lungs were normal. The blood pressure was 104/70. The abdomen was distended; the liver was not palpable. The spleen was enlarged. The right lower quadrant of the abdomen was tender to palpation. A routine blood count and the urine were normal. Examination of the stools showed a marked increase in fat (50 per cent of intake), with some occult blood and undigested food. The oral glucose tolerance curve was flat. Gastric analysis revealed achlorhydria after histamine stimulation. Duodenal aspiration demonstrated adequate amounts of pancreatic enzymes. X-ray studies of the small bowel revealed a disordered mucosal pattern and decreased motor activity.

The results of the fat-balance studies are shown in Table 1. After the initial studies the patient was placed on metabolic balance with a diet containing approximately 100 gm. of fat a day. Fecal fat was determined quantitatively in 5-day stool pools. After 2 periods, and before steroid administration was begun, severe abdominal pain, necessitating laparotomy, developed. A perforation of the jejunum was found and sutured. The suspected diagnosis of ileojejunitis was then proved by biopsy. Nine days after he recovered, the balance study was resumed. He was given



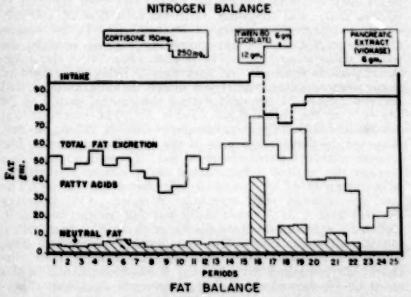


FIGURE 2. *Effect of Cortisone, Tween-80 and Pancreatic Extract in Case 3.*

cortisone intramuscularly, beginning with 250 mg. daily. On this regimen, fat excretion gradually diminished to 28 per cent of intake daily compared to 50 per cent during the control periods. Treatment had to be interrupted after 4 periods because acute intestinal obstruction developed. This was caused by a stenosis in the ileum, and operation was required. Sixteen days after recovery from this operation ACTH in doses of 60 to 80 mg. daily was administered for 3 periods, but fecal fat excretion rose slowly to 60 per cent of intake. The dietary fat had been reduced to approximately 50 gm. daily. When cortisone in doses of 100 mg. daily was added the fecal fat fell to approximately 25 per cent of intake. He felt extremely well and was discharged, to take 50 mg. of cortisone daily as a maintenance dose. After an interval of 42 days he was again studied in the Metabolic Unit during 4 5-day periods. During this study he was given 90 gm. of fat daily. Fat excretion was found to have remained at a fairly constant level of 20 to 25 per cent of intake, despite the increase in fat intake.

With the exception of the acute surgical episodes the patient improved considerably. He gained weight, the fever subsided, and the diarrhea stopped. However, a significant steatorrhea persisted even though adequate doses of ACTH and cortisone were administered and full pharmacologic effects were obtained. He became euphoric under treatment. "Moon face," acne, rapid weight gain and ankle edema developed. Hypopotassemia was observed. The eosinophil count dropped markedly.

The patient was discharged, and cortisone was discontinued. He re-entered the hospital a few months later with a fulminating recurrence of the ileojejunitis, from which he died shortly.

TABLE 2. *Effect of Cortisone on the Steatorrhea of Nontropical Sprue, As Measured by Comparison of Dietary and Fecal Fat.*

PERIOD	DIETARY FAT	FECAL FAT	FECAL FAT	CORTISONE
	gm./day	*gm./day*	*% of intake*	*mg.*
1 (Feb. 13-20)	96	84	87	—
2 (Apr. 7-14)	60	26	43	80*
3 (Apr. 14-21)	60	22	36	50*

*Cortisone given continuously from Feb. 25.

CASE 3. C.F.B., a 58-year-old man, gave a history of recurrent episodes of abdominal distress, frequently associated with nausea and vomiting, of at least 10 years' duration. Before 1947 he had been using alcohol to excess. During that year he noticed increasing frequency of bowel movements. The stools were white and oily. In 1948 calcified areas in the region of the pancreas were demonstrated on x-ray examination. In 1949 he began to take pancreatic extract with his meals, but the fatty diarrhea persisted. Acute exacerbations of the chronic pancreatitis recurred frequently. In March, 1952, he was admitted to the Veterans Administration Hospital, Los Angeles.

Physical examination revealed an emaciated, chronically ill man weighing 104 pounds. There was bilateral aphakia as a result of cataract operations performed 13 years previously. The heart and lungs were normal. The blood pressure was 118/80. The epigastrium was tender, but there was no muscular rigidity. The spleen and liver were not palpable. The prostate was enlarged. There was generalized atrophy of the muscles of all extremities, with ataxia of the lower extremities, which a neurologist considered to be due to a degenerative spinal-cord disease of unknown cause.

Examination of the blood showed a red-cell count of 4,500,000, with a hematocrit of 45.5 per cent, and a white-cell count of 7100, with a normal differential. The eosinophil count was 137 per cubic millimeter. Urinalysis was negative. The glucose tolerance curve was 115 mg. per 100 cc. fasting, 139 mg. at 30 minutes, 163 mg. at 1 hour, 180 mg. at 2 hours and 178 mg. at 3 hours. There was no glycosuria. The serum calcium was 9 mg., and the inorganic phosphorus 4 mg. per 100 cc. Gastric analysis demonstrated normal amounts of free hydrochloric acid after histamine stimulation. A duodenal drainage showed that there was marked reduction in lipase, proteolytic enzymes and amylase. X-ray examination disclosed extensive calcification in the region of the pancreas. A gastrointestinal series revealed motor dysfunction of the small bowel. A liver biopsy showed normal architecture, without fatty metamorphosis.

The results of the fat-balance study are shown in Figure 2. The patient was placed on a diet containing 100 gm.

of fat daily. After 4 control periods cortisone was given for 8 periods of 5 days each; 150 mg. was administered intramuscularly during the 1st 5 periods, and 250 mg. during the remaining 3. Fecal fat decreased during the 8th, 9th and 10th periods from 55 to 35 per cent of intake. From the 10th period on, the fecal fat rose again to the pretreatment levels of 50 to 55 per cent, even though the amount of cortisone was increased from 150 to 250 mg. daily. There was no effect on fat absorption from Tween-80, but pancreatic extract caused a marked fall in fat as well as nitrogen excretion. During the periods of treatment with cortisone the patient gained over 16 pounds in weight because

A B

FIGURE 3. *Appearance of Patient in Case 4 before* (A) *and Three Months after Treatment* (B), *When She Had Received Cortisone for Fifty Days.*

of water retention. He promptly lost it within 2 days of the discontinuance of cortisone. The eosinophils dropped from 137 to 20 per cubic millimeter. The nitrogen balance was negative throughout most of the period of cortisone administration. When this was stopped it gradually returned to equilibrium, and then became positive, as it was during the control periods.

There was no evidence that this patient with steatorrhea due to chronic pancreatitis responded to cortisone with any significant or consistent increase of fat absorption.

CASE 4. E.M., a 29-year-old housewife, first noticed diarrhea in 1945. She gradually lost 40 pounds and complained of increasing weakness. In 1947 and 1948 she had 2 normal pregnancies. During these two years she recovered normal health and was asymptomatic. Diarrhea, with light-yellow, foamy stools, recurred in 1949. In the course of the next 2 years her weight dropped from 150 to 67 pounds. She was admitted to the Veterans Administration Hospital in Los Angeles in January, 1952, when she complained of poor vision at night and rawness of the mouth. She noticed that she bruised very easily. Cramps in the hands and feet occurred frequently. She was nauseated and vomited after meals. She had diarrhea, with 8 to 10 voluminous stools daily. She had not had any menstrual periods for the preceding 18 months.

Physical examination revealed a severely emaciated, acutely ill woman weighing 67 pounds. The temperature and pulse were normal; the blood pressure was 82/64. The skin of the face, neck and hands was hyperpigmented. The breasts were atrophied. The heart and lungs were normal. The abdomen was protuberant, and the liver edge was palpable 4 fingerbreadths below the right costal margin and was smooth, soft and nontender. The spleen was not felt. There was moderate edema of both ankles. All tendon reflexes were hyperactive. The hair of the axilla and pubis was scanty (Fig. 3*A*).

Examination of the blood showed a red-cell count of 2,800,000, with hemoglobin 6.4 gm. per 100 cc.; the hematocrit was 21 per cent, the mean corpuscular volume 100 cubic microns, the mean corpuscular hemoglobin 28 micromicrogm., and the mean corpuscular hemoglobin concentration 28 per cent. Urinalysis was negative. Urinary ketosteroids were 4.4 mg. per 24 hours. The serum calcium was 8.8 mg., the serum phosphorus 1.7 mg., the serum albumin 3.96 gm., and the serum globulin 1.84 gm. per 100 cc. Glucose tolerance was 74 mg. per 100 cc. fasting, 89 mg. at ½ hour, 58 mg. at 1 hour, 62 mg. at 2 hours and 86 mg. at 3 hours. The prothrombin time was 58 per cent of normal. Other liver-function tests were negative. Gastric analysis revealed free hydrochloric acid in low normal amounts. The fecal fat was 84 per cent of the ingested fat. A bone-marrow biopsy was negative. A liver biopsy disclosed fatty metamorphosis. X-ray studies of the gastrointestinal tract demonstrated hypomotility and greatly disordered motor function. Transit time of the barium meal through the colon was delayed. A survey of the bones revealed advanced osteoporosis.

Initially, the patient was treated with a high-calorie diet containing 150 gm. of protein and approximately 100 gm. of fat, with supplementary vitamins, iron and calcium for the correction of specific deficiencies. However, neither folic acid nor vitamin B_{12} had any effect on the anemia. Her general condition improved slowly. She gained 23 pounds in 2 months. The blood count improved, and the electrolytes and prothrombin time returned to normal. However, the steatorrhea remained unchanged, and she did not improve further. The dietary fat intake was then reduced to 60 gm. daily, and cortisone instituted in a dose of 100 mg. daily. Subjective improvement was striking. In the course of the next 2½ months she gained another 35 pounds, the weight rising from 105 to 140 pounds (Fig. 3*B*). Her menstrual periods returned. At that time 2 7-day collections of stools were obtained, and it was shown that the fecal fat had decreased from 84 per cent during the control period to 36 per cent of the ingested fat (Table 2). The cortisone was gradually reduced to a maintenance dose of 25 mg. a day. However, no further lowering of the fecal fat occurred. The glucose tolerance curve remained flat. Throughout cortisone therapy the patient demonstrated the common side effects, with "moon face," acne and considerable pedal edema. The last was relieved with mercurial diuretics. On discharge she still had 4 to 5 stools daily but felt subjectively well. Cortisone was omitted on discharge from the hospital, 6 months after admission. She was given a gluten-free diet, which she followed carefully. Eighteen months after discharge she remained entirely well. X-ray examination of the small bowel showed that all the abnormal signs had disappeared. A stool fat analysis revealed 23 per cent of dry weight, an amount of fat within normal limits. All the laboratory abnormalities found during the period of hospitalization had reverted to normal. When gluten in the form of wheat was given during a 2-month period, when she was in complete remission, she stated that there was slight bloating and "gas," but no diarrhea or other adverse effects.

DISCUSSION

The influence of adrenal hormones on absorption of fat from the intestine has been under investigation for many years. Conflicting opinions have been of-

fered on the basis of animal and clinical experiments. Verzár and McDougall[8] observed that fecal fat excretion in rats increased after operative removal of the adrenal glands. On the other hand Barnes et al.[9] studied the absorption of corn oil and its esters from the intestinal tract of adrenalectomized rats and were unable to demonstrate any impairment. Stillman and his associates[10] found that incorporation of radioactive phosphorus into the phospholipid molecule continued at normal rates and quantities in adrenalectomized rats; this process of phosphorylation occurred equally in the presence of decompensated adrenal insufficiency and in rats with adrenal insufficiency but on a high sodium chloride intake. They therefore concluded that this phase of fat absorption from the intestine was not influenced by the action of adrenocortical hormones.

Clinical similarity between Addison's disease and the sprue syndrome has led to the opinion that adrenal insufficiency may be responsible for the deficient fat absorption in the sprue syndrome. In both conditions patients complain of weakness and fatigue. Weight loss and hyperpigmentation are noted. The blood pressure is low; diarrhea occurs in both, and Addison's crises are said to bear some resemblance to acute exacerbations of sprue.[6] There is impairment of carbohydrate absorption in both diseases. Fat-absorption curves, as determined by the vitamin A tolerance test, improved in a case of Addison's disease after therapy with cortisone.[1] Diéz Rivas et al.,[11] in their investigation of patients with sprue in remission, concluded that 40 per cent demonstrated decreased adrenocortical activity. This observation was based on abnormal Kepler water tests and Cutler–Wilder tests, low urinary 17-ketosteroid levels and abnormal Thorn tests. They examined the adrenal glands of 13 patients who had died of sprue, and found atrophy of the cortex, with depletion of cortical lipids, in all cases. Adlersberg and his associates[5] described atrophy of the adrenal cortex in sprue but reported no specific lesions.

With the advent of cortisone, ACTH and hydrocortisone potent drugs for the treatment of sprue became available. ACTH was also found to be effective in Whipple's disease.[12] Colcher, Drachman and Adlersberg[6] state that the reduction of steatorrhea in these conditions by the use of these agents supports the contention that an impairment of adrenocortical reserve was a factor in the increased fecal fat excretion. In support of this theory is cited the evident clinical improvement of patients with sprue refractory to all other types of treatment. Patients kept in remission on maintenance doses of cortisone or ACTH relapsed within one to five weeks when these drugs were discontinued. On reinstitution of ACTH or cortisone clinical improvement was again observed. Improved vitamin A tolerance tests suggested a direct effect of ACTH on intestinal absorption of fat. It was concluded that changes of glucose tolerance and vitamin A absorption were due to the action of ACTH or cortisone on the intestinal mucosal cells.[12] However, fat-tolerance curves give a composite picture of absorption, metabolism and storage. Therefore, an improved serum vitamin A level may indicate changes in storage or degradation as well as in absorption. Furthermore, fat-absorption curves in the serum vary from day to day in the same person to such a degree that it is impossible to draw valid conclusions from isolated determinations.

Increased blood flow to the intestinal mucosa and improved contact due to increased motility have been considered responsible for improved absorption. It has been demonstrated by direct absorption studies in segments of intestine closed off with balloons that, with induced hyperperistalsis, sugar and dl-methionine are absorbed in greater quantities.[13] Wade[14] reported that improvement in patients with celiac disease after the use of laxatives and posterior pituitary extracts was due to the improvement of intestinal peristalsis. It is known that peristalsis in sprue is markedly hypoactive. Therefore, it can be assumed that, in the course of restoring better health, more normal peristalsis will occur. This in itself may be a factor in improved absorption.

The clinical observations militating against the direct effect of ACTH and cortisone on intestinal fat absorption are numerous. Paniagua et al.[15] found normal adrenocortical reserve in patients with sprue. Almy[16] reported an eosinopenia in severe cases of sprue demonstrating an adequate stress response. Intravenous administration of ACTH over eight-hour periods resulting in an adequate adrenocortical stimulation failed to improve vitamin A absorption curves in patients with sprue.[1] According to Taylor et al.[2] fecal fat decreased in 6 patients with sprue treated with cortisone, but in only 1 did the levels approach normal. Giansiracusa and his associates[17] reported that, in the face of striking clinical improvement in 2 patients with sprue on ACTH, 1 showed unchanged fat excretion, and 1 showed higher fecal fat than before treatment. Thorn and his co-workers[18] stated that a short course of adrenal-hormone therapy in a case of pancreatic insufficiency failed to modify the severity of steatorrhea. In summary it may be said that there are several theories regarding the influence of cortisone and ACTH on fat absorption and that the methods of study may not take all these mechanisms into account.

In the course of steroid therapy euphoria and a sense of well-being accompany the improvement in appetite and weight gain. The beneficial changes of a raised blood pressure, raised blood sugar, increased peristalsis, increased metabolic rate and reduction of inflammatory and fibroblastic reaction all undoubtedly have a major part in the general clinical improvement. In Addison's disease small doses of cortisone

restore normal salt retention. An increase beyond the needed dose brings about an imbalance of the physiologic state into the opposite direction, resulting in excessive salt retention. Therefore, if a deficiency of cortical hormones were the cause of the steatorrhea in sprue and if fat absorption were influenced by the steroid hormones, it might be expected that the excessive amounts of steroids administered would not only correct the malabsorption but also reduce fecal fat below the normal level. This, however, did not occur in the cases presented above. In the steatorrhea that follows gastrectomy the intestinal mucosa is intact, and split fat is available for absorption. If the intestine could be stimulated to greater fat absorption by administration of steroids in large quantities this effect should occur in steatorrhea of this type. However, no improvement was observed. Normal fecal fat levels could not be obtained in the patient with sprue. About four or five times the normal amount of fecal fat persisted for the entire period while the patient was on cortisone.

The contention that ACTH and cortisone may have had a specific effect on the intestinal mucosa of the patients with sprue and ileitis cannot be categorically denied. However, it seems more likely that the intestine shared in the general improvement of the body tissues and that fat absorption improved together with the general restoration of normal metabolic processes in the entire body.

Our findings support the conclusion of authors who do not subscribe to the theory of a direct effect of adrenocortical steroids on fat absorption.

Summary

The effect of ACTH and cortisone on steatorrhea in 4 patients with different diseases was investigated by means of fat-balance studies over a prolonged period.

The steatorrhea in 1 patient with pancreatic insufficiency and in 1 with a partial gastrectomy was not modified by ACTH or cortisone.

A patient with intestinal malabsorption secondary to chronic ileojejunitis improved with ACTH and cortisone. Another patient with nontropical sprue improved markedly on treatment with cortisone. Although fecal fat excretion was reduced in each case it remained abnormally high. It is believed that the improvement in these 2 cases may reflect a general metabolic restoration rather than a specific effect on the absorptive capacity of the intestine.

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THE HEMATOCRIT OF CAPILLARY BLOOD*

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THE measurement of the packed red-cell volume (or hematocrit) of the venous blood has long been recognized as a useful aid in the study of blood in a large number of clinical conditions. The technic described by Wintrobe[1] in 1929, using venous blood, has gained almost universal acceptance and is regarded as one of the simplest and most reliable of methods. Its value is further enhanced in that the commonly accepted "normal values" for the mean red-cell volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration have been calculated, using packed-cell-volume levels determined by the Wintrobe[2] technic.

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However, this valuable tool for the study of blood diseases is seldom used when dealing with infants and small children because of the difficulty of obtaining samples of venous blood. Many alternative methods for measuring the hematocrit devised over the years required either capillary or very small quantities of venous blood. Most of these procedures have had drawbacks, either in design or in application, that have prevented them from gaining widespread acceptance.[3]

In 1934 Guest and Siler[4] reported a micromethod for the determination of the packed cell volume of capillary blood. The present study is an evaluation of that method, with the use of commercially available apparatus.

In the present study the method described permits the hematocrit to be measured easily with the use of capillary blood. Briefly, it has the advantages of requiring very small samples of capillary blood, involving only five minutes of centrifugation, being technically simple to perform and giving reproducible, accurate results that are virtually interchangeable with Wintrobe readings.

Materials

Blood

Capillary blood obtained from a finger (or oxalated venous blood, if available) is used.

Tubes*

These are capillary tubes, 75 mm. long and approximately 2 mm. in diameter ("melting-point tubes"), containing dried heparin. The tubes are discarded after use.

Centrifuge†

This consists of a disklike head with a diameter of 19 cm. (7.5 inches). Twenty-four numbered radial slots are cut in the head to accommodate the capillary tubes, the sealed ends of which rest against a retaining rim at the periphery of the disk. The head has a close-fitting, detachable cover, which provides streamlining and keeps the tubes from being thrown out during centrifugation. The head locks onto the shaft of a high-speed (10,000-r.p.m.) electric motor by means of a spigot so that removal of the cover releases the head from the drive shaft, thus enabling it to be used as a carrier for tubes before centrifuging. A timing device is built into the unit, and the whole instrument is enclosed in a strong safety shield.

*Capillary Tubes-Heparinized (Cat. No. 23922), available from Aloe Scientific Division of A. S. Aloe Company, St. Louis, Missouri.

†International Hemacrit Centrifuge, available from International Equipment Company, Boston.

Microhematocrit Reader‡

This device, designed by one of us (A.R.J.) will be fully described in a later communication. It consists of a holder that permits the capillary tube to be radially positioned above a disk on which a logarithmic spiral is engraved. A second disk, mounted below the first on a common axis, bears on its periphery a logarithmic radial scale in the range 1.0 to 100.0. The disks may be rotated independently. In operation the part of the logarithmic spiral that cuts the plasma level in the capillary tube is found by rotation of the upper disk. The 100.0 graduation on the lower disk is set opposite a reference line on the tube holder, and then both disks are rotated together until the spiral line cuts the red-cell level in the tube. The graduation on the lower disk that falls opposite the reference line at this instant represents the hematocrit reading directly expressed as percentage of red cells.

Technic

A sharp stab with a lancet is made in a finger that has been cleansed with 70 per cent alcohol. The first drop of blood to appear is wiped away with a sterile dry gauze. A free flow of blood is obtained by slight compression of the finger proximal to the puncture, and a capillary tube is filled by gravity to within 1 or 2 cm. of the end. The unfilled end of the glass tube is heat sealed by being held perpendicular to and just touching the outer margin of a microburner gas flame for two to four seconds. Constant rotation of the tube is necessary during the sealing process to ensure that the inner base of the tube will be flat rather than tapered.

One quickly becomes expert in this maneuver. Until such a time, however, it is advisable to fill at least 2 capillary tubes so that if the sealing process is faulty, the other tube can be used. If the tube is held too long in the flame a bubble will form, and the tube must be discarded. If the tube is not rotated properly the inner base will be tapered, and the tube must also be discarded since both these conditions will lead to an inaccurate reading. The patients' names should be listed and numbered on a sheet of paper, and as the tubes are collected, they can be placed horizontally in the correspondingly numbered slots in the portable, lightweight centrifuge head. Once sealed, the tube should be so placed that the sealed end lies just in contact with the peripheral rim of the centrifuge head. Since the centrifuge accelerates very rapidly it will cause glass to shatter if the glass is propelled even 1 or 2 mm. by centrifugal force. Hence, it is essential that the glass be in contact with the metal and not 1 or 2 mm. away from it.

Once all the glass tubes are inserted, the flat, re-

‡Available from International Equipment Company, Boston.

movable centrifuge head cover may be screwed in place; the tubes need not be balanced in this centrifuge, nor need they be placed opposite one another. This permits an odd number of samples to be run at a time if one so desires. The automatic timing device goes into operation as the motor is turned on. The timer should be set for five minutes, at which time the motor is automatically turned off. If the hematocrit cannot be read promptly the tubes are set in a vertical position, with precautions to ensure their identity, because slanting of the packed cell column occurs if the tube is left in the horizontal position for more than thirty minutes.

Experimental Studies

Two criteria must be fulfilled to establish the validity of any new method for determining the hematocrit level: the procedure must yield reproducible results, and it must bear a constant relation to the established and universally accepted Wintrobe method.

Reproducibility

We measured the reproducibility of our results with the microhematocrit technic by simultaneously spinning many capillary tubes filled from the same sample of oxalated venous blood. Three subjects were used, each having a different packed red-cell volume, and, in all, 61 microhematocrit determinations were made. The reproducibility of our results with the Wintrobe method was also investigated. Four subjects were used, each having a different volume of packed cells, and, in all, 49 Wintrobe hematocrit determinations were made. The data are presented in Table 1.

The coefficient of variation was from 1 to 3 per cent when the microhematocrit method was used and from 1 to 2.7 per cent when the Wintrobe method was used. In both procedures the variation was 1 per cent when the hematocrit was about 45 per cent. The figure varied between 2 and 3 per cent when the hematocrit was lower. It is apparent that, in our hands, the microhematocrit method yields as reproducible results as the Wintrobe method.

Table 1 also contains values derived by other workers using a different microhematocrit method and the Wintrobe method. These data also show coefficients of variation of 1 per cent when the hematocrit is about 45 per cent.

The variability in the microhematocrit levels encountered when as many as three tubes were filled from the same finger was studied, as was the variability in results when the blood was obtained from different fingers of the same hand. Three subjects were used for this phase of the study, each having a different packed cell volume; in all, 22 hematocrit levels were determined on capillary blood by means of the microhematocrit method. There were essentially no differences in the packed cell volume of capillary blood regardless of which finger was used or the number of tubes filled from each finger.

Table 1. *Reproducibility of Determinations of Packed Red-Cell Volume with the Microhematocrit and Wintrobe Methods.*

Source of Data	Patient	No. of Observations	Packed Cell Volume			
			Mean	Standard Deviation	Coefficient of Variation	Range
Present study —microtechnic	A	15	31.9	±0.95	3.0	30.0-33.8
	B	24	43.5	±0.42	1.0	43.0-44.5
	C	22	30.9	±0.71	2.3	30.0-32.5
McIntroy[3] (1954)	1	20	20.6	±0.3	1.5	Not given
—microtechnic	2	20	46.7	0.5	1.0	Not given
Present study	D	14	37.2	±0.69	1.9	36.0-38.0
—Wintrobe method	E	12	44.7	±0.45	1.0	44.0-45.0
	F	11	34.7	±0.68	1.9	34.0-36.0
	G	12	33.4	±0.89	2.7	33.0-34.0
Biggs & Macmillan[3] (1948) —Wintrobe method		50	45.5	±0.4	1.0	Not given

Comparison with the Wintrobe Method

With the technic described, the hematocrit of capillary blood was determined in 100 infants and children seen in the Research Hematology Laboratory at the Children's Medical Center. Oxalated venous blood was also obtained from each of these subjects, and, simultaneously, the hematocrit of the venous blood was determined by the technic just described as well as by the conventional Wintrobe method.

The hematocrit levels of these 100 bloods as determined by the Wintrobe method varied from 16 to 63 per cent. The details of the distribution are shown in Table 2, which also indicates the corresponding levels obtained by the microhematocrit method. Figure 1 is a plot of the packed red-cell

volume as determined by the microhematocrit versus that as determined by the Wintrobe method.

It is clear that the microhematocrit levels closely approximate the Wintrobe hematocrit levels throughout the observed range and that a straight line may be fitted to the points in Figure 1. Hence, there is a constant, easily defined relation between the levels obtained by the two methods.

TABLE 2. *Wintrobe Hematocrit Levels of 100 Samples of Venous Blood and the Mean Values of the Corresponding Microhematocrit Levels.*

No. of Samples	Hematocrit with Wintrobe Method	Hematocrit with Micromethod	
		Venous blood	Capillary blood
	%	%	%
1	16.0	14.8	14.8
1	18.0	17.5	15.8
1	19.0	19.5	18.0
1	26.0	26.0	25.0
1	29.0	28.0	27.0
2	31.0	30.0	28.0
2	32.0	35.0	34.0
1	33.0	36.0	34.0
2	34.0	32.0	31.0
1	35.0	36.0	34.0
3	36.0	33.3	32.8
7	37.0	36.5	36.5
8	38.0	36.5	37.0
3	38.5	37.4	37.0
13	39.0	37.8	37.8
10	40.0	38.6	38.2
11	41.0	39.8	39.6
2	41.5	39.0	39.5
5	42.0	40.5	40.0
1	42.5	40.0	38.5
7	43.0	41.6	40.0
3	44.0	42.5	41.2
3	45.0	43.4	40.4
1	46.0	46.0	45.0
4	47.0	45.5	47.0
2	48.0	44.5	44.0
1	57.0	56.0	58.0
1	62.0	60.0	64.0

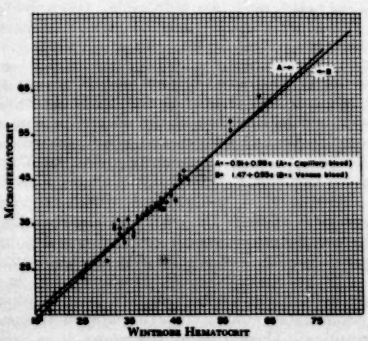

FIGURE 1. *Packed Cell Volume, As Determined by Microhematocrit and Wintrobe Methods.*

The mean packed red-cell volumes of the 100 patients obtained by each of the three determinations are presented in Table 3. This table also shows the correlation coefficients between the values obtained by the Wintrobe method and those obtained by each of the microhematocrit determinations.

TABLE 3. *Comparison of the Mean Packed Cell Volume in 100 Consecutive Patients, As Determined Simultaneously by Three Methods.*

Method	Mean ± Standard Error of Mean	Mean Difference between Wintrobe & Indicated Methods ± Standard Error of Difference	Correlation Coefficient between Wintrobe & Indicated Methods
Capillary blood in microhematocrit tubes	37.9 ±0.6	−1.7 ±0.2	0.933
Venous blood in microhematocrit tubes	38.3 ±0.6	−1.2 ±0.2	0.957
Venous blood in Wintrobe tubes	39.6 ±0.6		

The Wintrobe method yields a significantly higher packed cell volume than either of the microhematocrit methods ($P < 0.001$). It must be emphasized, however, that, although the differences between the means are statistically significant, they are so small

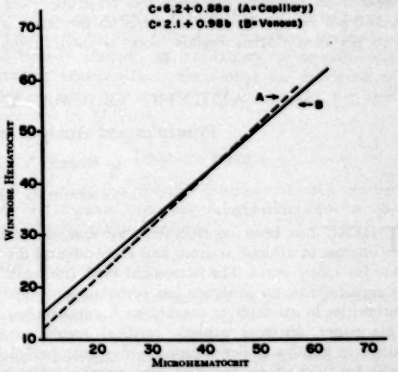

FIGURE 2. *Nomogram for Conversion of Microhematocrit to Wintrobe Hematocrit Levels.*

— 1.7 and 1.3, respectively (Table 3) — that they are without practical significance.

The correlation coefficients (Table 3) between each of the microhematocrit determinations and the Wintrobe hematocrit determination are very high: 0.933 when capillary blood is used and 0.957 when venous blood is used in the microhematocrit. Therefore, microhematocrit levels predicted from Wintrobe levels or, vice versa, Wintrobe hematocrit levels predicted from microhematocrit levels will be very close to, if not identical with, the observed values. The predicted values for the microhematocrit levels

would be based on the equations derived to describe the distributions represented in Figure 1. These are

$$a = -0.91 + 0.98\,c \quad (1)$$
$$\text{and } b = 1.47 + 0.93\,c \quad (2)$$

where a = the microhematocrit level using capillary blood; b = the microhematocrit level using venous blood; and c = the Wintrobe hematocrit level. The equations for predicting the Wintrobe hematocrit level from the microcapillary hematocrit level are

$$c = 6.2 + 0.88\,a \quad (3)$$
$$\text{and } c = 2.1 + 0.98\,b \quad (4)$$

where a, b and c have the same meanings as those given above.

The nomograms corresponding to equations (3) and (4) are presented in Figure 2. They may be used to convert the microhematocrit levels to the corresponding Wintrobe level.

It is worth noting that the packed cell volumes ranging from 35 to 55 per cent, as determined by the microhematocrit, do not differ from the predicted Wintrobe packed cell volumes by more than 2 units. When the microhematocrit level of capillary blood is 35 per cent the predicted Wintrobe value is 37.0 per cent; when the former is 55 the latter is 54.6 per cent. When venous blood is used in the microhematocrit the predicted Wintrobe hematocrit levels at the corresponding points are 36.5 and 56.0 per cent respectively.

Summary and Conclusions

The microhematocrit method is a dependable one that gives highly reproducible results.

In the microhematocrit method described, venous or capillary blood may be used interchangeably. In either event the results are comparable to those obtained when the Wintrobe technic is used.

Only five minutes of centrifugation are required, and the technical aspects of collecting and processing the blood are quite simple.

We are indebted to Dr. Louis K. Diamond, director of the Hematology Research Laboratory and the Blood Grouping Laboratory, Children's Medical Center, for guidance in the design of the experiment and for helpful criticisms.

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ATHLETIC TRAUMA AND INCIDENTAL DISEASE

Principles and Analysis at Boston College, 1950-1955

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THERE has been considerable lay and medical interest in athletic trauma and its incidental disease for many years. The occasional fatal traumatic or medical case in athletics has stimulated medical authorities in attempts to prevent such catastrophes. This paper discusses athletic medical results obtained at Boston College during a five-year period, 1950 to 1955. Nine hundred and twenty athletes participated in varsity competitive football, hockey, track, basketball and baseball. The current collegiate and general medical literature on athletics has been reviewed.[1-11]

Screening

The athletic-team physician at Boston College is responsible to the faculty chairman of the Athletic Board. The Athletic Medical Department consists of 3 physicians, a trainer and an assistant trainer. During this five-year period the policy has been to have one of the trained first-aid men present at all college games and practice sessions involving bodily contact and to have one of the doctors present at all contact football sessions and games, as well as all hockey games. As recommended by the Third National Conference of Health in Colleges, a medical history is taken, and physical examination, urinalysis, x-ray study of the chest and electrocardiography are performed on all athletes annually, before participation. The history, physical examination and urine and x-ray examinations are repeated on a yearly basis. Electrocardiograms are taken only on first examination, unless clinical symptoms indicate a repetition. These clinical procedures have confirmed the axiom that the medical history and physical examination are most important factors in determining the health of an athletic participant.

From findings of these screening examinations 5 athletes were ruled out permanently from athletic participation. One, who was found to have a tumor of the testicle, was referred to his family doctor for follow-up study and treatment. A central type of

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early infectious arthritis was discovered in a candidate for track. Two athletes presented clinical histories of old rheumatic fever, with organic evidence of persisting heart murmur and definite histories of early congestive changes during exertion. The fifth was found to have acquired a clinical lumbar-disk syndrome incurred while working on a summer construction job.

Disqualification because of Injury or Illness

During this five-year period the Medical Department noted 448 injuries or illnesses during athletic participation that resulted in some degree of temporary or permanent disqualification. This represented a 48.7 per cent rate of injury or coincidental illness during athletes' participating time. This is in contrast to a 70 per cent figure cited in the literature by McPhee[7] during his analysis of a ten-year period of athletic injuries and illness at Princeton. The lower figure may be explained by the fact that it represents only injuries and illness that disqualified a participant for a specified period.

There were 10 cases of injury and 1 of illness associated with athletic participation that caused the Medical Department to rule that these athletes should not participate further in athletics. Nine of these occurred in football, 1 in hockey, and 1 in basketball.

Two football players sustained neck injuries of sufficient gravity to rule out further participation. One of these was associated with unilateral nerve signs that made it possible to make a diagnosis of a cervical-disk injury that was later borne out at operation. The second athlete sustained a high facet injury of the first and second cervical vertebras, with minor subluxation on severe stress. Both these injuries were diagnosed early, and no disability followed extensive medical care and consultations. Three players were separated from the squad because of shoulder dislocations. One of these was due to a glenoid fracture sustained during participation in athletics outside Boston College; it left a joint instability of such a character that repeated dislocations occurred. Two patients had initial and repeated shoulder dislocations. In each case the initial injury was treated conservatively, but repeated episodes occurred on minor stress. One of these required a surgical operation because of the amount of existing capsule defect. Another football player was disqualified because of 2 concussions in varsity competition; he had a history of a previous concussion in high school. Bilateral transient sciatica affecting the leg occurred in another case, with x-ray evidence of a congenital anomaly of the lower back with spondylolisthesis. Still another athlete had a severe repeated injury to the gastrocnemius tendon, with anterior hemorrhage that ossified and gave him an impairment of ankle-joint function. The ninth football participant had an attack of moderately acute ulcerative colitis during the preseason practice sessions.

The hockey player noted the onset of precordial chest pain of a suffocating type that lasted for a period of several hours after tournament play at high altitude in Colorado. He was hospitalized, and electrocardiograms revealed persistent abnormal tracings on three occasions over a period of a week that were consistent with myocardial ischemia. Although consultation and medical follow-up study gave no definite evidence of infarction, the occurrence of such a syndrome in a young athlete was considered to make further athletic participation inadvisable.

The basketball player had to discontinue further participation because of an old back epiphysitis, with scoliosis and pain.

When one considers that 7 of the football cases occurred without predisposing factors involved, the rate of football injuries of sufficient extent to rule out further football participation on a permanent basis becomes 1.3 in 100. This figure compares very closely to that of 1 in 100 reported by McPhee[7] in his ten-year analysis of football injuries at Princeton. Medical records reveal that 22 athletes, predominantly football players, with a small percentage of hockey players, were disabled for a particular athletic season. This represented an incidence of 4.4 per cent in comparison to one of 3.1 per cent reported by McPhee.[7]

Types of Injury

Regarding the specific injuries incurred during athletic trauma necessary information can be obtained from medical records.

Knee Injuries

There were 49 knee injuries, of which 5 required open operation. All these injuries were treated in a routine, conservative manner, with freedom from weight bearing, compression bandages and ice applied during the early minutes of the injury. Aspiration of fluid within the joint was not practiced; heat applications and natural absorption of the joint fluids constituted the prevailing policy at all times. The more severe knee injuries were associated with a considerable number of tears of the medial collateral ligament, partial and complete; the percentage of cartilage injury in these cases was low, and conservative treatment resulted in cures in most of them. Of the 5 operations only 3 were done for pure cartilage injuries, and good results were obtained in all; in 1 of these an osteochondritis of the medial femoral condyle was revealed (no doubt a result of the extreme stress that the knees of a heavy lineman sustain in football action since the same process has

been considered to exist in the arthritis found on x-ray study on knees of many football players, particularly linemen). The last knee operation was for a calcified pretibial bursitis. The rate of approximately 10 per cent of operations for these knee injuries compares closely with that cited by McPhee.[7]

Ankle Injuries

Thirty-four ankle injuries were noted during this period, with 4 established fractures. One injury was associated with 2 different injuries to the gastrocnemius tendon, with calcification of a blood clot posterior to the capsule of the ankle; this was later operated on for removal of the calcified hematoma. Clinically, it was the opinion of the Medical Department that the more severe ankle sprains, of which there were many, were the tears of the anterior tibiofibula ligament described by Thorndike.[3] These particular injuries required a minimum of two or three weeks for recovery and had a tendency to recur in a chronic form. Routine strapping of ankles during contact stress has been considered a great aid in the prevention of ankle strains.

Injuries of Adductor Thigh Tendons

There were 5 injuries of the adductor thigh tendon, with 1 that caused an extensive iliac retroperitoneal hematoma and false signs of an acute surgical abdomen for two or three days. These were recognized as such; careful hospital observation ruled out indication for laparotomy.

Neck Injuries

There were 8 neck injuries of significant extent; the 2 described above involved permanent separation from contact football. The remainder were ligament strains, and the patients recovered completely in seven to fourteen days.

Concussions

Ten concussions of significant extent were recorded; 1 is described above. All the patients were observed closely in the hospital, with appropriate neurosurgical consultations and electroencephalography.

Shoulder Injuries

There were 12 significant contused shoulder injuries. These responded well to routine heat therapy and careful preservation of motion range under treatment. In 4 cases residual traumatic bursitis and tendonitis about the shoulder were noted. There were 6 shoulder dislocations; 3 of the more severe ones are described above.

Acromioclavicular Separations

Approximately 6 acromioclavicular separations were noted during this time; only 1 was complete. None of these patients were operated on, and all obtained excellent results.

Fractures

There were 44 fractures, 4 of the ankle (medial or bimalleolar), 1 (compound) of the tibia and fibula, 3 of the lumbar transverse processes, 1 of the foot (scaphoid), 14 of the nose, 2 of metatarsals and 3 of metacarpals, 3 of the wrist (navicular), 1 of the humerus, 4 of phalanges, 1 of the sternum, 2 of the radius, 2 of the zygoma and 3 of ribs.

One rib fracture had excessive callus that produced an x-ray picture compatible with a chondroma; the rib was resected to eliminate the possibility of such a tumor.

Navicular fractures of the wrist were based on old high-school injuries in 2 of the 3 reported cases. In 1 case a small fragment was removed surgically.

The 1 recorded fracture of the sternum had a traumatic effect on the heart as confirmed by abnormal electrocardiograph tracings; the examination was indicated because of peculiar chest symptoms associated with a mild febrile reaction over a period of several days. It was considered that the heart made a full recovery; the patient was allowed participation after a one-year rest, and had no recurrence of the symptoms.

There was 1 severe compound comminuted fracture of the tibia and fibula during a football game. Two days later a severe viral infection made its first clinical appearance. After a clinically stormy course the patient made a complete recovery.

Nasal fractures, when recognized as having any disability or obstruction, were treated immediately, and nose-guard protection provided subsequently. Four plastic repairs of the nose were performed after the completion of the senior year in cases in which there was persisting cosmetic nasal deformity.

Contusions

Six extensive thigh contusions were recorded, of which 2 consisted of severe transection of the quadriceps muscle in its body portion. One patient recovered on conservative therapy after approximately three months; the other required surgical repair at a later date with a fascia-lata transplant, with a good clinical result. Two other quadriceps contusions were of the paretic variety; one was associated with a persisting causalgia that took four months to be cured.

Ten contusions about the abdomen and anterior hip required careful hospital surgical observation to rule out any associated injury to an intra-abdominal viscus. In 1 of these cases a contused-liver syndrome was diagnosed, and surgery was avoided by means of careful continuous attention with a good result. Fortunately, there was no case of ruptured spleen, although 2 patients were watched very closely for this syndrome. Numerous contusions of other por-

tions of the body were sustained; some of these were associated with large hematomas, which were treated in routine conservative fashion.

Back Injuries

Fourteen back injuries were observed during this period. Of these, 1 (described above) caused permanent withdrawal from participation in football. Another patient had a history of a lumbar-disk syndrome in high-school football that had been treated by competent orthopedic care, with a good clinical recovery; because of normal findings and the patient's eagerness to participate again in football, he was permitted to do so without further difficulty. One athlete, mentioned above, had a classic acute disk syndrome sustained during heavy lifting for a construction company in the summer. In 4 other back injuries of this group there was evidence of an unstable lower back, with congenital anomalies of joint articulations. These patients, however, responded to care and recovered fully after a year's separation from football. All 4 were able to resume football in the following year without further difficulties.

Discussion

In the period under consideration numerous examples of spontaneous severe disease and illness have occurred in athletes during participation. Several acute, severe viral infections, varying from systemic influenza and gastroenteritis to infectious mononucleosis, occurred. Interestingly enough 6 distinct syndromes of neurocirculatory asthenia were observed during this period, none of which prevented participation in contact sports. All these patients manifested a distinct lack of sustained stamina while in actual sports participation. Organic heart disease can occur before participation in sports, and it is wise to screen it out. Functional heart symptoms, as described above, may also be detected in association with trauma. Participation in sports in such cases was not permitted until the opinions of medical and cardiac consultants had been obtained.

Summary

The medical policies and methods of the Boston College Athletic Department are described. The reasons for permanent and temporary disqualification for participation in sports are enumerated. Clinical findings concerning the specific injuries that a body sustains during athletic trauma are discussed. Reference is made to coincidental disease occurring during participation in athletics.

On the basis of medical screening during seasonal participation in sports, athletes with conditions regarded as medical risks are removed from body-contact sports. This policy is believed to have prevented severe and perhaps even fatal medical accidents.

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USE OF MORPHINE IN TERMINATING CHILLS AND AS AN ANTIPYRETIC

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FOURTEEN years ago I gave 10 mg. of morphine intravenously to a woman with severe abdominal pain and a shaking chill due to a septic abortion. The chill promptly stopped. A short while later the patient thanked me, noting that the pain had actually been more endurable than the chill and that she was glad that I had been able to stop the chill. When, several days later, another patient presented herself at the hospital with a shaking chill in addition to pain from a huge gluteal abscess, I decided again to give morphine intravenously for the pain, but more specifically to note its effect, if any, on the chill; 10 mg. of morphine was followed by prompt cessation of the chill.

This paper reports my clinical experience with the use of morphine in terminating chills and presents data showing that morphine has a definite antipyretic action that is of use in therapeutics.

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Review of the Literature

I have been unable to find any reference in the literature concerning the use of the opium alkaloids for the termination of chills in human beings. Magne[1]

reported the termination of shivering in dogs exposed to a low environmental temperature with 0.05 mg. of apomorphine per kilogram of body weight.

An antipyretic action of the opium alkaloids was first noted by Manassein[2] in 1869. He reported that the usual hyperpyrexia (0.5 to 0.8°C.) — that he obtained by injecting putrid fluid into fasting rabbits — did not occur when the rabbit had been given 120 mg. of morphine. He also found that, when the narcosis abated too rapidly, the fever made its appearance, but was not as high as that in non-narcotized rabbits. Since Manassein first made his observations, other workers[3-8] have found morphine to have an antipyretic action in rabbits and dogs. It must be noted that with but two exceptions[3,4] narcotizing doses of morphine were used.

TABLE 1. *Diagnosis in 56 Cases of Chill Treated with Morphine.*

DIAGNOSIS	NO. OF CASES
Transfusion & plasma reaction	14
Cellulitis; lymphangitis.	9
Malaria, therapeutic	8
Reaction to intravenous infusion of fluid	5
Reaction to typhoid vaccine	3
Septic abortion	3
Pneumonia	3
Septicemia	2
Malaria	2
Drug fever	2
Subacute bacterial endocarditis	1
Mercuhydrin reaction	1
Pyelonephritis	1
Gluteal abscess	1
Perirectal abscess	1

Regarding the antipyretic action of morphine in human patients, Preisendörfer,[9] in 1880, described a case of advanced tuberculosis with fever in which 30 mg. of morphine was given and in which the temperature ninety minutes later was found to have dropped 0.6°C. In 1914 von den Velden[10] reported the effect of morphine and codeine on the temperature of patients with croupous pneumonia. In 5 cases he noted a fall in body temperature of 0.8 to 2.1°C. in two or three hours.

CLINICAL STUDIES

Termination of Chill Reactions

Perera,[11] in an excellent review of the subject, notes that "to both physician and layman, a chill represents a serious and alarming sign." I would add further that a chill, aside from being an alarming sign, is one of the most unpleasant symptoms of disease that a patient must endure. It is quite surprising, therefore, that not until 1938, when Beeson and Hoagland[12] reported the use of calcium chloride for the relief of chills, was an agent available to the physician for the alleviation of this most distressing symptom. In their hands calcium chloride intravenously terminated chills in the majority of cases, but they noted no antipyretic action of the drug. In my own experience calcium chloride frequently failed to terminate a chill, probably because of very slow instillation of the chemical in an endeavor to avoid cardiac syncope or hypotension. In addition to the potential dangers from a cardiac point of view calcium chloride has the drawbacks of frequently causing a phlebitis and also marked tissue destruction if the substance is injected outside the vein. These factors, in my opinion, make calcium chloride an agent far from ideal for the termination of chills.

Intravenous administration of morphine is relatively free from danger when used judiciously.[13] In my own experience the procedure has had no untoward reactions, and in every case the chill was promptly terminated.

The cases for which morphine intravenously was used fell into two groups. In the first group were patients in whom the chill was associated with a rising body temperature, and in the second group were those in whom the chill was associated with a presumptively normal or falling body temperature.

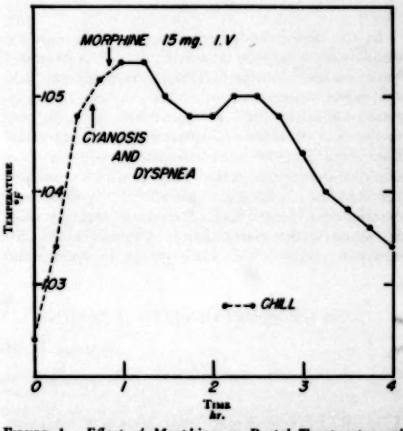

FIGURE 1. *Effect of Morphine on Rectal Temperature of a Patient Given Malaria Treatment for Paresis.*

The types of cases in the first group, along with the underlying pathologic state, are listed in Table 1.

In the second group were 30 acute battle casualties seen shortly after injury. Three patients had severe burns, and 27 had wounds of varying severity

from shell fragments. In all cases pain was the indication for morphine, but chill reactions of varying degree and from a variety of causes, such as shock, fright and low environmental temperature, ceased promptly after the instillation, intravenously, of 15 to 30 mg. of morphine.

Antipyretic Use

Although reported in the literature[9,10] the use of morphine as an antipyretic agent has found little acceptance by the medical profession. This is quite understandable since hydrotherapy and the chemical antipyretics have in ordinary circumstance proved highly efficacious. There are situations, however, in which I have found morphine to be the more ideal antipyretic agent — namely, in cases in which it is desirous to stop immediately any further increase in body temperature. Such a circumstance is shown in Figure 1. The patient, receiving malaria treatment for general paresis, suddenly became cyanotic and dyspneic during a paroxysm. The temperature at this time was 104.8°F., and he was having a chill. It was

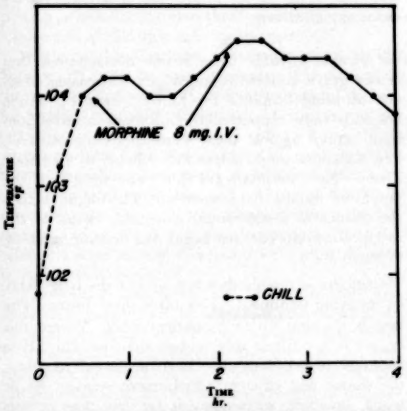

Figure 2. *Control of Rectal Temperature and Chills in Artificially Induced Fever by Means of Morphine.*

imperative to stop the chill and reduce the fever immediately. Morphine accomplished both promptly.

Another use for morphine is shown in Figure 2. During a malarial paroxysm morphine in small doses used at the appropriate time can keep the fever within bounds so that the patient is spared the deleterious effects of fever above 105°F. and yet obtains the advantages of malaria therapy with the temperature in the range of 104°F.

If morphine is given early in the malarial paroxysm and the dosage is relatively large, it is possible to prevent the chill and suppress the fever. Typical fever curves to illustrate this are found in Figures 3 and 4.

In the use of triple typhoid vaccine for fever therapy it was found that if morphine was given subcutaneously before or intravenously with the vaccine, the expected febrile response did not occur.

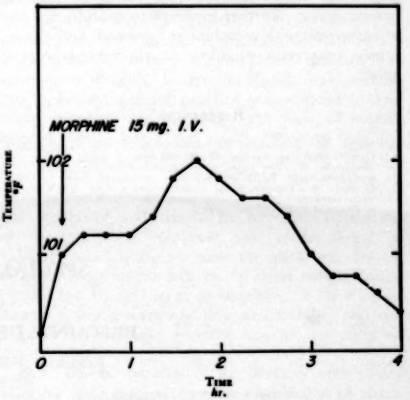

Figure 3. *Temperature (Rectal) Curves in Artificial Malaria Controlled by Morphine.*

Summary and Conclusions

A hitherto undescribed action of morphine—namely, its ability to terminate a chill—is noted. An experience in which this action of morphine invariably gave prompt and comforting relief to patients having a

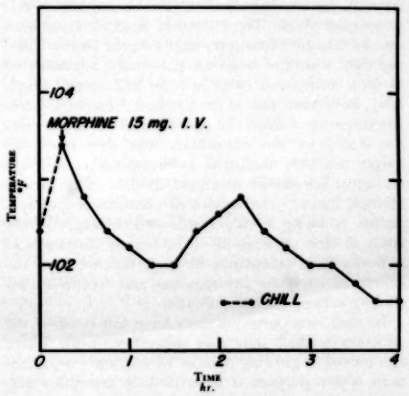

Figure 4. *Effect of Morphine on Rectal Temperature and Chills in Paroxysms of Artificially Induced Malaria Therapy.*

chill and was unattended by adverse reactions is described; the termination of a chill was accomplished with 8 to 30 mg. of morphine given intravenously.

It is not well known that morphine has an antipyretic action. Further evidence to confirm the fact of antipyresis with morphine is furnished, and its usefulness in certain situations in clinical medicine is noted.

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SPECIAL ARTICLE

BRITAIN'S HEALTH SERVICE

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THE British National Health Service being now in its seventh year, the present is a fitting time to take stock of the position. It should first be said unequivocally that the Health Service is firmly, and so far as can be seen, permanently established in the national life. There is not the smallest doubt that to the individual patient it is of immense benefit. All classes, and particularly the middle class, are freed from all anxiety regarding the cost of any illness that may befall them. The voluntary hospitals have been saved from the bankruptcy that awaited them. They, together with the hospitals previously administered by local authorities (such as fever and mental hospitals), have been placed on a sound democratic basis. No longer does their size and efficiency depend upon the wealth of the community that they serve; no longer are they managed by irresponsible and obscurantist busybodies who hold the fate of physicians in their hands. The service of consultants and specialists is being evenly distributed throughout the land, so that patients living in remote districts and suffering from complaints however obscure have the benefit of adequate investigation and treatment, including subsequent rehabilitation.

In their new form hospitals have lost none of the affection in which they have always been held. There are, indeed, a growing number of voluntary organizations whose purpose it is to provide amenities that are outside governmental scope. In many places "Friends of the Hospital" provide minor amenities such as tennis courts for nurses. But although this is the general attitude there is one development that causes grave concern—namely, the increasing practice of suing hospitals for faulty treatment. When hospitals were supported by voluntary contributions legal actions against them were almost unheard of. Few solicitors would allow their clients to take such a step. Now hospitals are fair game since it is the taxpayers' money that is involved. The litigant stands the chance of a substantial gain and, owing to the recently introduced Free Legal Aid Scheme, nothing to lose.

Criticism is mainly directed against the long delay in receiving treatment. This takes three forms. The first is queuing up in outpatient halls. Where this occurs it is entirely due to bad management. It is confined to hospitals that have neglected to adopt the simple and efficient appointment system. At its worst, however, such delay is far less than it was under the old system. Complaint is made that some specialists are inexcusably unpunctual in their attendance.

Secondly there is delay in obtaining an appointment. It is quite usual for a patient suffering from a comparatively simple complaint to have to wait as long as two months. General practitioners are accused of referring patients to hospitals without sufficient reason. On the other hand specialists tend to be obsessed with the desire for perfection, preferring the exhaustive examination of the few to the slightly less exhaustive examination of the many, regardless of the principle of the greatest good to the greatest number.

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Thirdly, there is delay in admission to the wards. This is very serious and is mainly due to financial considerations to be mentioned later. Urgent cases are naturally admitted before the nonurgent, with the result that long-stay patients such as old people with fractured femurs impede the rapid turnover of short-stay cases.

General Practitioners

General practitioners, now that their financial claims have been met, seem to be well satisfied. If they have more forms to fill up they are at least relieved from bookkeeping and bad debts, and from the embarrassment of having to limit their attendance according to their patients' pockets. All necessary drugs are theirs to give. Pathologic and roentgenologic examinations are becoming more readily available to them, and a start has been made in the provision of various ancillary bodies such as health workers whose function it is to look after the home conditions of patients. Encouragement is being given to group practice (a more natural and less costly development than the health centers originally proposed), which should give them greater freedom for leisure and attendance at refresher courses.

Much has been written concerning abuse of the Service. It may be said, however, that now that the novelty has worn off demands upon physicians for trivial complaints, arising out of a desire to get something for nothing, are made only by a few. Such people at least have the excuse that early recourse to the physician is constantly dinned into their ears by advocates of early diagnosis. Abuse of this kind, moreover, was by no means unknown under the old system, and it was the universal experience that the offenders were usually those who were most dilatory in paying their accounts.

Two minor complaints are made. In the first place some patients are inclined to dictate treatment: "I want penicillin" or "I want to see a specialist." It is, of course, only natural that the right to free treatment should encourage aggressive behavior, but physicians should have sufficient strength of character to resist it. Secondly, middle-class patients tend to resent the disappearance of the preferential treatment and the minor amenities to which direct payment for services previously entitled them. I should say at once that the Service has not resulted in any deterioration in the physicians' attitude toward their patients. If they now have less time to sit and gossip with those of their own class it is because of the increased work thrown upon them. They have, too, responded well to the spirit of the times by improving their equipment and the accommodation and amenities of their offices.

Entry into Practice

Apart from complaints that the three branches of the Service—general practice, hospitals and the work administered by local authorities—are not sufficiently co-ordinated, the general working of the Service gives satisfaction. Serious problems have, however, arisen. These concern entry into both general and consultant practice. It may seem surprising that, at a time when general practitioners are working harder than ever, entry into practice was never more difficult. Before the Health Service came into operation general practice was entered in two ways: purchase and squatting. Purchase, of course, needed capital, but a loan could always be obtained on terms that were by no means onerous. To the Labour Government the idea that the welfare of patients should be determined by a physician's pocket was anathema, and, despite the strenuous opposition of the profession, purchase was made illegal, a "global" sum* being set aside for good will. Squatting and waiting for patients to come was a slower process but by no means unsuccessful. I have never known a young doctor of reasonable ability and enterprise fail to make good by one or the other of these methods.

Now, one of the aims of the Service (and a very laudable one) is to equalize the distribution of physicians over the country so that areas are served according to their needs rather than their wealth. Areas have therefore been designated "overdoctored" or "underdoctored." Only in the latter is squatting permitted, the squatter being given a smaller grant to last him while he builds up a list of patients. In all areas, when a vacancy occurs through death or retirement, the post is advertised, and the successor selected by a local committee. The virtual limitation of the number of practices, combined with the increasing number of physicians desiring them, means that hundreds of physicians are doomed to spend the best years of their lives as assistants or locum tenentes. Owing to the capitation system of payment principals are naturally reluctant to take assistants into partnership. The amount of distress thus caused can be gauged from the fact there may be 50 or 60 applicants for a vacancy. One cause of the trouble, it is said, is that physicians are reluctant to practice in the North, where amenities are fewer and the climate less agreeable. The difficulty could be solved by reducing the maximum number of patients from 3500 to 2500, a step desirable on other grounds. But this could not be done without an increase in the capitation fee that would certainly be resisted by the taxpayer.

The abolition of the purchase of practices also affects the exchange of practices. Previously, a physician, considering himself too old to continue in a large industrial practice, could easily exchange it for a small practice in a seaside resort. Such an exchange can still be made, but only with great difficulty.

*A "global" sum of money equivalent to the estimated value of all the general practices in Great Britain in 1948 was set aside by the Government to compensate general practitioners for the loss of the salable value of their practices; on retirement they were to receive this sum.

Registrars

In hospitals an analogous difficulty affects the registrars. Concerning these a word of explanation is necessary. Before the war registrars were among the senior interns. They were few in number, a large teaching hospital having about 3 — 1 in medicine, 1 in surgery and 1 in obstetrics. The posts were held for one or two years and were regarded as stepping-stones to the honorary staff. Holders who were unsuccessful in realizing this ambition went into general practice in a provincial town, where their special experience enabled them in due course to practice their specialty as consultants in the local hospital.

At the end of the war the Ministry of Health created a large number of registrarships, partly to make good the abnormal number of retirements and partly to provide the advanced training that promising young physicians had lost through service in the armed forces. Their number has been further increased by the augmented demand for consultants created by the Health Service. These registrars are now considered essential to the hospital service, every consultant having one or two of them. They assist him in his work and act on his behalf during his absence.

Unfortunately, this increase in the number of registrars has not been accompanied by an equivalent increase in the number of consultant posts, with the result that only a small proportion, estimated at about 1:10, of the registrars have any chance of permanent establishment. The plight of these unfortunates, many of them approaching middle age with wives and families, is indeed heart-rending. General practice is virtually closed to them because there are sufficient competitors from among assistants in general practice and because their training has lain in an entirely different direction. So most of them are reduced to the dreary round of applying for one permanent post after another. Even in towns of 150,000 there may be as many as 70 applicants where perhaps there would have been only 1 or 2 before the war.

This problem is naturally arousing a good deal of thought. One solution suggested is the creation of a number of subordinate permanent posts. It is a reflection on modern civilization that so many highly skilled persons should be doomed to live more than half their lives before attaining to positions of complete independence and full responsibility. Some general practitioners think that in the smaller hospitals registrars are quite unnecessary and that the work could be done by themselves in the capacity of part-time clinical assistants as was done before the war.

Too Many Doctors?

In short, therefore, both in general and in hospital practice the Health Service is a very good thing for the established, but for the unestablished it can be grim in the extreme. This only shows the unexpected problems that arise when the law of supply and demand is superseded by central planning. The question naturally arises whether too many doctors are being trained. The unpopularity of the Health Service at the outset led many people to predict that the number of entrants would drop. Actually, the reverse happened. Numbers increased greatly in all the medical schools and were far in excess of places. This was due partly to the strong hereditary tendency in the profession and partly to the fact that the youths of the period, having grown up in an atmosphere of insecurity, preferred the security of a nationalized profession to the insecurity of a commercial career. They could not know that security in medicine was by no means guaranteed.

These considerations have led the Government to appoint a committee charged with the task of estimating long-term requirements with a view to adjusting the intake accordingly. How formidable is the committee's task need hardly be mentioned — there are so many unknown factors, among them medical progress, population trends and national wealth. So long as Treasury allocation to the Service remains unaltered any increase in personnel obviously means hardship to existing physicians. Another complication is that as medicine becomes increasingly technologic, and as the physician becomes increasingly dependent upon lay assistants in the form of biochemists, laboratory assistants, dietitians, electrocardiographers and a host of others, the time may well come when the State prefers the cheap labor of the technician to the more expensive labor of the physician.

Many medical students, perhaps the majority, are maintained by the State. They can therefore be said to be sponsored by the State. The logical conclusion therefore seems to be that the State is under an obligation to find employment for them for the whole of their working lives or, if they are prematurely superannuated, to provide them with substantial pensions. The Health Service would thus come into line with the rest of the Civil Service and with the Fighting Services. It must be realized that the Health Service is unique among Services in that its participants are for the most part allowed to engage in private practice. The *logical* solution, therefore, may well be a full-time salaried service, which is the one thing that most members of the profession dread. Britons have the reputation of disliking logic and are said by foreigners to have a genius for making the illogical work. Some solution on the present lines and permitting the continuance of private practice may be found. Two things, however, should be noted: difficulties involving hardship to individuals will increase rather than decrease; and, in this security-loving age, the rising generation fears a full-time service far less than their fathers do.

The Cost

Having dealt with the effect upon the profession one may pass to the question of cost, which, after all, is the crux of the matter. It so happened that the Health Service was established at a time when medicine had embarked upon its phase of accelerating expansion. Subsequent expansion has been due, not as the politicians boast, to their activities, but to further scientific progress, though the Service has facilitated the more general diffusion and application of such progress. The certainty that this accelerating expansion will continue makes further rises in the cost of treatment inevitable. At the same time the benefit to the nation that can be attributed to the Health Service is impossible to estimate. From the undoubted benefit to the patient in the form of more efficient treatment of the successive illnesses to which he is liable it is generally concluded that national health is improving — that is, the total quantity of ill-health existing at any given moment is declining. But this is quite illusory. Man being mortal, the decrease in acute diseases must result in an increase in chronic diseases, especially those affecting the aged. And since by definition the latter last longer than the former the result is the strange paradox of improvement in individual health coexisting with deterioration in national health. As I have said elsewhere this is in an age of medicated survival.

This truth is far beyond the comprehension of the politicians. Yet even they have been forcibly awakened from their pipe dream that the Health Service would lead to a diminution in the amount and therefore in the cost of ill-health. The present Government has been unable to prevent a rise in cost, although a small one, above the ceiling set by its Labour predecessor. Charges have had to be imposed. Not until the year 1957-1958 will it be possible to embark on substantial additions and replacements of hospital buildings, and even then at a rate slower than before the war. Meanwhile, obsolescence increases running expenses. The problem of the accommodation of the increasing number of the aged sick is accentuated by the difficulty that their younger relatives find in looking after them. Alarmed at the future the Government last year appointed a Royal Commission to go into the matter. Its report is now awaited with great interest. It is a measure of the magnitude of the problem that it should have been found necessary to take this step despite the elaborate administrative machinery that already exists.

The growth in the health needs of the community is due to the advance of civilization and would have arisen if there had been no health service. This country believes that the problems caused by such growth are met better by a health service than by the previous system. But one disadvantage of the Health Service is that it masks the dependence of its efficiency upon national income. The relation between individual medicine and individual wealth is obvious, but the relation between national medicine and national wealth is something that the average person finds difficult to grasp, especially in a period of commercial prosperity like the present. Health has become something to which everyone has a right irrespective of his contribution to national wealth. It is lamentable that those who so readily use the strike weapon fail to see that the withholding of their labor, with however just a reason, cannot fail to diminish national income, upon which alone the Health Service depends. One cannot help having grave misgivings about what would happen in the event of a serious recession in trade.

The immense spending power of the masses, estimated at £2,200,000,000 on alcohol, tobacco, movies, television, betting and football pools, might be regarded as a reserve to be drawn upon as the cost of the Health Service mounts. But this is not how things work out. Civilization becomes enslaved to the high standard of living that it has created for itself, and strenuously resists the curtailment of the amenities to which it has become accustomed.

The Labor Problem

But more serious than the problem of cost is the problem of labor. Many thousands of beds are out of use owing to shortage of nurses. It is no exaggeration to say that if it were not for immigrants from Southern Ireland, France, Italy, Germany and the countries of the Commonwealth the fever and mental services would completely break down and the position of other hospitals would be made very difficult. *We have more ill-health than can be dealt with by our own nationals.* For the efficient treatment of our sick we depend upon people from countries whose standard of health is much lower than our own. This to my mind is a humiliating position for a great country. Through our wealth we are able to buy this foreign labor. This shows that the standard of medical treatment in a country is determined by wealth rather than by needs, a fact that runs counter to the idealist's dream of equalizing medical services throughout the world.

Bad as the labor situation is now, it will become infinitely worse in the future. Thirty years hence females of working age will have decreased by 500,000 whereas males will have increased by approximately the same number. But this prospect, so far from being an argument against a health service, may be regarded as an argument in its favor, for the most economical use of a limited supply of labor is probably better secured by a nationalized than by a free system.

Summary

I have tried to give a balanced account of the Health Service. While stressing its merits I have in-

dicated its failings, the difficulties under which it labors, the efforts being made to overcome these difficulties and the problems that the future will bring. I may say that so far the Service works much better than many of us expected. Unfortunately, many Americans have condemned it outright. In doing so they have, I suggest, failed to take cognizance of the difference between the American and the British temperament. I end as I began by assuring Americans that, for better or worse, the British Health Service has come to stay.

MEDICAL PROGRESS

THE HUMAN HEMOGLOBINS IN HEALTH AND DISEASE*

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IN 1949 Pauling and his associates[1] described sickle-cell hemoglobin and introduced into medicine the concept of the molecular disease, a concept that implies that certain diseases are caused by genetically determined abnormalities of protein synthesis. Progress in the study of the human hemoglobins, and of the molecular diseases that they cause, has been so rapid in the past six years that it seems advisable to review the available information in this field and to attempt a correlation of the many clinical and hematologic observations related to these syndromes.

TABLE 1. *Recommended Nomenclature for Hemoglobin Types.*

NOMENCLATURE*	SYNONYMS & TERMS PREVIOUSLY USED
Hgb A	Normal Adult Hgb; Hgb N; Hgb a.
Hgb F	Fetal Hgb; Hgb f.
Hgb S	Sickle-Cell Hgb; Hgb b.
Hgb C	Hgb III; Hgb c; Hgb X.
Hgb D	———
Hgb E	———
Hgb G	———
Hgb H	———

*As recommended by special committee of Hematology Study Section, United States Public Health Service, January, 1953.

Several excellent reviews of the biochemical aspects of the abnormal hemoglobins have appeared during the past few years.[2-5] Furthermore, two extensive summaries of sickle-cell anemia[6,7] and one of the clinical and hematologic findings in the sickle-cell variants have also been published.[8] This communication is therefore limited to a short review of some of the more important differentiating characteristics of the human hemoglobins and to a systematic presentation of the knowledge concerning the various diseases due to these abnormal pigments. No extensive discussion of the clinical characteristics of the hereditary hemolytic syndromes is undertaken.

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NOMENCLATURE

In 1953, under the auspices of the Hematology Study Section of the United States Public Health Service, a group of interested investigators met to decide on a standard system of nomenclature to avoid the confusing aspects of terminology that have plagued many other fields of investigative work, particularly those related to hematologic research.[9] On the recommendations of the committee, the following system was adopted:

Normal adult hemoglobin	Hgb A
Normal fetal hemoglobin	Hgb F
Sickle-cell hemoglobin	Hgb S

All other hemoglobin types are referred to by capital letters of the alphabet starting with "C", skipping the letters "F" and "S". The letter "B" was omitted for two reasons: Hgb S had in the past been called Hgb b by some investigators,[8] and Hgb C and Hgb D were already established entities at the time the current recommendations were agreed upon.[10,11] At present, 8 hemoglobin types have been described; these are listed in Table 1, with some of the symbols previously used to identify them.

For some time it has been the practice in this laboratory, as well as in the laboratories of others, to designate syndromes involving several hemoglobin types by listing the major pigment component first. Thus, sickle-cell trait is given the formula Hgb A plus Hgb S since the former compound usually comprises over 55 per cent of the total hemoglobin mass. The advisability of adopting this system seems clear when one realizes that both the Hgb C trait and the disease caused by the occurrence of thalassemia minor and Hgb C in the same person have hemoglobin patterns that contain Hgb A and Hgb C. In Hgb C trait, however, Hgb A predominates so that the designation Hgb A plus Hgb C is appropriate, whereas in thalassemia-Hgb C disease the reverse is true; the latter, therefore, is designated as Hgb C plus Hgb A. In all

references to the hemoglobin syndromes in this paper the major hemoglobin component appears first irrespective of the apparent importance of the minor hemoglobin fraction in determining the name or hematologic characteristics of the disease.

Biochemistry of Human Hemoglobin Types

Although several of the human hemoglobin types possess distinctive biochemical properties the exact way in which these pigments differ remains an unsolved problem. All the human hemoglobins studied have identical molecular weights.[4] The isolated heme portions of the compounds about which information is available (Hgbs A, S and F) seem to be alike.[3,12,13] Quantitative differences in the amino acid composition of the globin portion of the molecule have not been striking[12,14-16] although they undoubtedly exist, at least for Hgb F.[16-18] More important seem to be suggested alterations in amino acid arrangement, types of end groups and the folding of the amino acid chains in the various hemoglobin molecules.[1,3,17] Such differences in the globin moiety of the molecule may explain many of the observations to be listed below. Finally, insufficient study has been given to the problem of possible alterations in the heme to globin linkages in the various hemoglobin types. Further investigation along these lines certainly seems to be indicated.

Table 2. *Comparative Biochemical Characteristics of the Human Hemoglobins.*

Name	Alkali Denaturation	Isoelectric Point	Anodic Mobility on Paper Electrophoresis (Relative)	Solubility of Reduced Hgb (Relative to Hgb A)	Ultraviolet Absorption Spectrum (Relative to Hgb A)	O_2 Dissociation Curve (Relative to Hgb A)	Immunologic Specificity
Hgb A	Normal	6.87	2	High	Normal	Normal	No
Hgb F	Alkali resistant	6.98	3	Higher than Hgb A	Abnormal	Abnormal	Yes
Hgb S	Normal	7.09	4	Very low	Normal	Normal	No
Hgb C	Normal	7.30	6	Higher than Hgb A	Normal	Normal	No data
Hgb D	Normal	7.09	4	Same as Hgb A	Normal	No data	No data
Hgb E	Normal	No data (probably >7.09)	5	Same as Hgb A	Normal	No data	No data
Hgb G	Normal	6.98	3	No data	No data	No data	No data
Hgb H	Normal	<6.87	1	No data	Normal	Normal	No data

Fetal Hemoglobin

Fetal hemoglobin (Hgb F) was first detected in 1866 by Körber,[19] who observed that hemoglobin solutions prepared from cord-blood erythrocytes were resistant to destruction or denaturation by highly alkaline solutions. Hemoglobin solutions prepared from normal adult erythrocytes were rapidly denatured under identical experimental conditions. Upon this difference in the rate of alkali denaturation is based a simple, rapid laboratory technic described below, for the demonstration and quantitative estimation of fetal hemoglobin.[20] Numerous other differences exist between Hgb F and Hgb A (Table 2). These have been extensively described by Lecks and Wohlman[2] and by White and Beaven.[4] The characterizing features may be summarized as follows:

Crystallographic differences, including evidence obtained as a result of x-ray diffraction studies.[21-25]

Differences in amino acid composition and arrangement. The embryonic pigment has distinctive amounts of at least three amino acids, particularly isolucine.[16,18] Furthermore, Hgb F has been found to have three more terminal valine residues and four more free lysine ϵ-amino groups than Hgb A.[17]

Differences in electrophoretic mobilities and isoelectric points.[26-29]

Spectrophotometric differences in the ultraviolet region where the tryptophane fine-structure band of Hgb F is located at 289.8 millimicrons and of Hgb A at 291.0 millimicrons.[28-30]

Differences between the rates at which Hgb A and Hgb F spread as a monomolecular film on the surface of a liquid.[31]

Solubility differences, which show that fetal hemoglobin is more soluble than Hgb A in strong phosphate buffer.[5,23,32-35]

Immunologic specificity.[36-39]

Differences in the oxygen dissociation curves, that of Hgb F being to the left of the curve for the normal adult compound.[40-43]

Different rates of coagulation by heat.[44]

Differences in the peroxidative activity of the two hemoglobins.[45]

Sickle-Cell Hemoglobin

Sickle-cell hemoglobin (Hgb S) possesses a number of characteristics that differentiate it from the normal adult pigment (Table 2). The epic-making discovery of Pauling et al.[1] demonstrated that Hgb S has a distinctive electrophoretic behavior. Under identical experimental conditions, utilizing a phosphate buffer of 0.1 ionic strength at pH 6.9, Hgb S migrates

as a positive ion whereas Hgb A migrates as a negative ion. These variations in mobility correspond to differences in the isoelectric points of the two compounds of approximately 0.22 pH units. Similar observations on the rate of migration in an electric field may be demonstrated by the use of the simple technic of paper electrophoresis, described below. In their reduced form, crystals of Hgb S are birefringent whereas those of Hgb A are not.[46,47] Although no marked differences in the total composition of basic and acidic amino acids have been found,[12,15,16,18,48] there is evidence that Hgb S has approximately one more reactive SH group per mole of hemoglobin than Hgb A.[49]

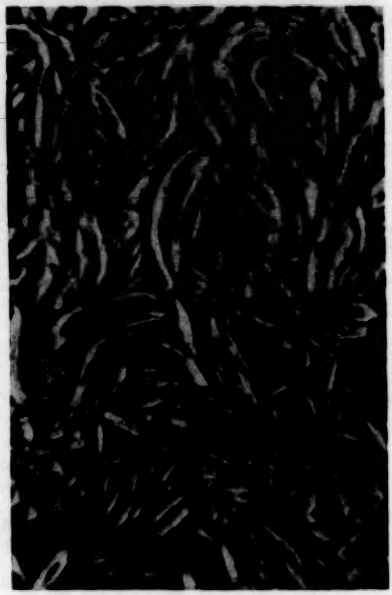


FIGURE 1. *Crystals (X 1400) of Reduced Hgb S (Tactoids) As Seen under the Phase Microscope (Reproduced from Singer and Chernoff[51] with the Permission of the Publishers).*

Perhaps most striking have been the observations related to the solubility of oxygenated and reduced Hgb S.[35,46,47,50] If one assigns an arbitrary value of 1 to the solubility of oxy-hemoglobin A, oxy-hemoglobin S is found to have the same solubility.[47] Reduced Hgb A has only half the solubility of its corresponding oxy-compound. Reduced Hgb S, on the other hand, is approximately 50 times less soluble than reduced Hgb A and has only a hundredth of the solubility of its oxy-compound. As a consequence of this insolubility a marked increase in viscosity takes place as concentrated solutions of Hgb S are reduced.[50] Indeed, after sufficient reduction, the entire hemoglobin mass forms a semisolid gel, which can be liquefied and solidified at will by the alternate use of oxygen and carbon dioxide.[50-52] When partially or completely reduced stroma-free solutions of Hgb S are examined under the phase microscope, crystals of a peculiar shape, called tactoids, are regularly observed[50,51] (Fig. 1). These Hgb S crystals have the appearance of crescents and strongly resemble sickled erythrocytes. The sickled erythrocyte is therefore, as Harris[50] has stated, "a hemoglobin tactoid thinly veiled and somewhat distorted by a red cell membrane." Upon this unique biochemical phenomenon, the striking insolubility of reduced Hgb S with the subsequent formation of sickle-shaped tactoids, depend all clinical tests for the demonstration of sickling.

No differences between Hgb S and Hgb A have been detected in their ultraviolet and visual absorption spectrums,[3] immunologic properties,[37,38] oxygen dissociation curves[53,54] or rate of alkali denaturation.[20]

Hgb C

Hgb C has been less extensively studied from a biochemical standpoint than Hgb F and Hgb S. The main distinguishing characteristic of Hgb C lies in its distinctive electrophoretic mobility, which indicates that Hgb C migrates as an ion even more positive than Hgb S.[10] The solubility of reduced Hgb C is greater than that of the reduced compounds of Hgbs F, S and A.[35] Hgb C and Hgb A cannot be differentiated on the basis of their oxygen dissociation curves,[55] ultraviolet and visible spectrums[55,56] and reaction to alkali denaturation.

Hgb D

Hgb D is an extremely rare type of hemoglobin, and few studies of its biochemical properties are available. Hgb D may be distinguished from other hemoglobin types, except Hgb S, by an electrophoretic mobility that is identical with that of the sickle-cell compound.[11] On the other hand Hgb D is much more soluble than Hgb S and thus may be differentiated from that pigment.[35] Reduced Hgb D is comparable in its solubility to reduced Hgb A. Tactoids, the gelling phenomenon and sickling cannot be elicited in cells containing Hgb D. In its alkali resistance Hgb D reacts in a manner similar to that of Hgbs A, S and C. Studies of other properties of this pigment have not yet appeared in the literature.

Hgb E

Hgb E can be differentiated electrophoretically from the other hemoglobin types.[57,58] The ultraviolet and visual absorption spectrums, solubility and resistance to alkali denaturation are similar to those of Hgb A.

Hgb G

Hgb G has been described in only two studies to date,[59,60] but at least two other possible examples of this compound have been detected.[61,62] Hgb G is characterized by an electrophoretic behavior identical with that of Hgb F.[59,60] Unlike that pigment, however, Hgb G is not resistant to denaturation by alkaline reagents. No results of studies on other properties of this compound are available.

Hgb H

Hgb H, observed in three generations of a single family by Page, Rucknagel and Jensen,[63] possesses a mobility on paper electrophoresis that is greater than that of Hgb A — that is, it is a more negatively charged compound than Hgb A.[63] The visual and ultraviolet absorption spectrums, oxygen dissociation curves and alkali resistance are the same as those for Hgb A.[64] Recently, another hemoglobin possessing a mobility greater than Hgb A has been described by Rigas, Koler and Osgood.[65] These investigators have also designated this compound as Hgb H.[65] Studies comparing these two pigments reveal a similar electrophoretic behavior at pH 8.6, but a marked dissimilarity at pH 7.0.[64] Furthermore, the Hgb H of Rigas et al. precipitates on standing, whereas that of Page and his co-workers does not.

Other Types

In addition to these compounds a number of hemoglobins have been observed that do not correspond completely to the types described above. It is becoming increasingly apparent, furthermore, that a whole spectrum of hemoglobin compounds probably exist that differ from each other in only minor respects. Only those which seem sufficiently distinctive, however, have been assigned identifying letters.

Table 2 summarizes the important physical and chemical features of the various forms of human hemoglobin.

Technics for Study of Human Hemoglobins

It is apparent from the foregoing discussion that numerous biochemical technics are employed in the characterization of the abnormal hemoglobins. In addition to the more specialized methods of solubility determinations, spectrophotometry, moving-boundary electrophoresis and so forth, two simple procedures may be utilized to identify most of the known hemoglobin types. These are the alkali denaturation procedure for fetal hemoglobin[20,29-31,66-73] and the technic of paper electrophoresis.[74-79]

Alkali Denaturation Technic for Hgb F*

Materials. These include, first, 2 to 4 cc. of unclotted anticoagulated (heparin, oxalate or sequestrene) venous blood. Then N/12 KOH is prepared as stock solution of standardized N/4 KOH and kept in a tightly stoppered paraffin bottle, 1 part of the stock solution being diluted to 2 parts of distilled H_2O for N/12 KOH. Finally, 50 per cent sat. $(NH_4)_2SO_4$ is prepared by the addition of 500 cc. of sat. $(NH_4)_2SO_4$ to 500 cc. of distilled H_2O plus 2.5 cc. of conc. HCl (11 N).

Procedure. Preparation of approximately 10 gm. per 100 cc. hemoglobin solution. The venous blood is washed once with physiologic saline solution and centrifuged, and the washings discarded. To 1 volume of the packed cells 1.5 volumes of distilled H_2O and 0.5 volume of toluene are added. This is shaken vigorously for two or three minutes and allowed to stand overnight in the cold at about 4-10° C.; if it is desirable to prepare the hemoglobin solution immediately the mixture is shaken for five or six minutes and refrigeration omitted. The mixture is centrifuged at 2000 to 2500 r.p.m for twenty minutes, and the upper clear layer and the middle layer of sediment are aspirated and discarded. The hemoglobin solution is filtered and used as is (solution A).

To carry out the technic of the test 0.1 cc. of the 10 gm. per 100 cc. hemoglobin solution (solution A) is pipetted into 1.6 cc. of the N/12 KOH contained in a Kahn tube. The 0.1-cc. blow-out pipette is rinsed five or six times with the KOH-hemoglobin mixture, which is agitated gently ten to twenty times. The reaction is permitted to proceed for exactly one minute and is stopped by the addition of 3.4 cc. of the 50 per cent sat. $(NH_4)_2SO_4$ solution. The Kahn tube is then inverted three or four times, and the mixture is filtered into a clean test tube (solution B).

Calculations. To calculate the percentage of Hgb F the optical density of solution B is determined in a colorimeter at 540 millimicrons, and this reading is related to the hemoglobin concentration in the original solution (solution A). In a Beckman spectrophotometer, the latter may be obtained by dilution of 0.02 cc. (Sahli pipetteful) of solution A with 4 cc. of distilled H_2O and reading at 540 millimicrons (solution C).

The percentage of Hgb F is obtained by the following ratio:

$$\frac{\frac{1}{4} \text{ optical density solution B}}{\text{optical density solution C}} \times 100 = \% \text{ Hgb F}$$

The factor ¼ is used because the hemoglobin in solution B is diluted 1 part in 50 whereas the dilution factor in solution C is 1:200, or solution B is four times as concentrated as solution C. In some colorimeters it may be necessary to use larger volumes of filtrate, which will alter the dilution factor employed in this calculation.

Comment. Evidence obtained as a result of immunologic, crystallographic, spectrophotometric and solubility studies indicate that the alkali-resistant hemoglobin is almost certainly identical with the normal

*Modified from Singer, Chernoff and Singer.[20]

fetal hemoglobin of the newborn infant.[20,38,80-86] It seems, therefore, appropriate to designate any alkali-resistant hemoglobin fraction as Hgb F, no matter how old the patient is at the time of examination. As discussed below, normal persons over the age of four or five have negligible quantities of fetal hemoglobin, and values of less than 2 per cent Hgb F are found by the alkali denaturation technic. With the concentrations described above under procedure, over 2.0 per cent Hgb F will impart a brownish to red color to solution B. This test may therefore be read without the use of a colorimeter to determine only the presence or absence of increased amounts of Hgb F.

FIGURE 2. *Electrophoresis Apparatus.*

Blood specimens from normal persons will appear colorless although spectrophotometric readings of up to 1.8 per cent alkali-resistant hemoglobin may be obtained on the colorless filtrate. It is not known whether this residual reading represents Hgb F or some other material, as yet unidentified.[20,87] However, since the alkali denaturation procedure is insensitive to less than 2 per cent Hgb F, all figures below that level are considered normal. Finally, the percentage of Hgb F determined by this procedure represents the amount of the fetal pigment left after one minute of reaction.[69] During this period all the normal hemoglobin, in addition to a small amount of Hgb F, is denatured. The discrepancy between the actual and observed values of Hgb F is small and is of no importance clinically.

Paper Electrophoresis*

Materials. First of all, 2 or 3 cc. of unclotted venous blood prepared as described above but diluted with H_2O to give a solution of approximately 5 gm. of hemoglobin per 100 cc. is required. Secondly, barbital buffer, pH 8.8, ionic strength 0.06, is prepared as stock solution, ionic strength 0.24, by dissolving 98.9 gm. of Na barbital and 11.1 gm. of barbituric acid in distilled H_2O and diluting to 2000 cc. To prepare a 0.06 ionic strength solution 1 part buffer is added to 3 parts H_2O.

Electrophoresis apparatus. A number of basically different electrophoretic apparatuses may be employed in this procedure.[74-79] Some utilize sheets or strips of filter paper suspended between bars or draped over a rod in the form of an inverted V. My coworkers and I have found most practical the use of a sheet of filter paper inserted between two glass plates (Fig. 2).[76] Siliconized glass plates, 9 15/16 inches x 14 inches x ¼ inch, are suspended between two buffer chambers made of Plexiglass. Each buffer chamber is divided by a partition into two sections, which are connected by a series of glass agar bridges. Carbon or platinum electrodes are placed in the outer receptacles, and the paper dips into the inner containers. A source of direct current, of approximately 300 to 400 volts, is used to supply the necessary power.

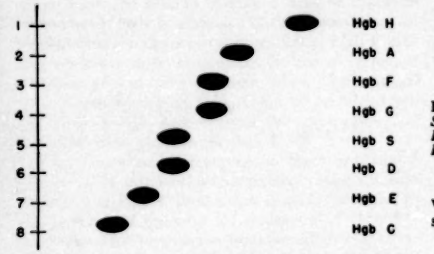
Procedure. Veronal buffer is placed in each of the four compartments to approximately the same height, and the level in the inner chambers is equalized by means of a tube joining the two units. The leveling tube is disconnected before the current is applied. The smooth side of a sheet of Whatman No. 3-MM paper, 18¾ inches x 9½ inches, is ruled vertically down the center, and crosslines placed at intervals of ⅝ or ¾ inch. The paper is then soaked in the buffer solution and blotted almost dry. From 0.002 to 0.005 cc. of the hemoglobin solution is applied at the crossmarks, and the paper placed between the dry, clean, siliconized plates. Six Hargraves No. 2† clamps apply firm, equal pressure to prevent puddling of the buffer. The plates and apparatus are then assembled, as in Figure 2, and approximately 350 volts of direct current applied. With a paper width of 9 ½ inches, from 14 to 16 milliamps of current will be drawn. The electrophoretic run is permitted to proceed for six to eight hours, at which time separation of the hemoglobins will be distinct enough for diagnostic purposes. To identify Hgb F or Hgb G it may be necessary to prolong electrophoresis to ten or twelve hours to achieve the necessary separation.[76] At the completion of the run the paper is dried rapidly in an oven at 100 to 130°C for an hour. To prevent uneven drying and movement of the hemoglobins by capillary action, one must be careful to have the paper in a horizontal position and suspended so that the area of the hemoglobin spots is not in contact with any surface. A convenient method is to wrap the paper about an icebox dish. With concentrations of 5 to 10 gm. of hemoglobin per 100 cc. of solution no staining is necessary to identify the components, but for a more permanent record the paper may be stained with bromphenol blue, which is prepared by dissolving 0.1 gm. of bromphenol blue and 10 gm. $HgCl_2$

*Modified from Smith and Conley.[76]

†Available from the Cincinnati Tool Company, Cincinnati, Ohio.

in 95 per cent ethyl alcohol to a final volume of 100 cc.[75] The dried paper is placed in the stain for ten minutes and washed free of excess dye with running tap water.

Comment. The patterns to be expected with the various hemoglobin types are schematically presented in Figure 3. Hgb H moves farthest toward the anode in the electric field of the paper[63] and is followed by Hgb A. Hgb F and Hgb G migrate somewhat more slowly and are imperfectly separated from Hgb A. Hgb S and Hgb D move less rapidly than Hgb F. Hgb E migrates even more slowly whereas Hgb C remains closest to the starting line. Hgb D, which is indistinguishable from Hgb S by paper electrophoresis, may be identified on the basis of solubility studies.[38] Hgb G may be differentiated from Hgb F by the resistance of the latter to alkali denaturation.[59] In practice, the hemoglobin compounds do not move as sharply as indicated on the schematic



Whatman No. 3-MM Filter Paper with Barbital Buffer at pH 8.8 and Ionic Strength 0.06. Run Carried Out for 8-10 hr. at 350 Volts (Direction of Anode to Right).

FIGURE 3. *Schematic Representation of the Hemoglobins, As Demonstrated by Paper Electrophoresis.*

drawing except when present almost completely free of other hemoglobin types (Fig. 4). When two or more pigments are present in the same blood specimen they appear to possess a mutual attraction on paper electrophoresis that alters their respective positions slightly[88] (Fig. 5). Despite this drawback the reliability of the technic is such that, when proper controls are used, rapid determination of the hemoglobin types may easily be achieved.

Recent observations suggest that the human hemoglobins may form a broad spectrum of compounds, each distinguished from its neighbor by only a slightly different position on paper electrophoresis. It will therefore become increasingly difficult to characterize future hemoglobin types by paper electrophoresis alone. Indeed, a number of pigments have already been observed that do not exactly fit established electrophoretic patterns. It is not known whether these represent new hemoglobins or whether the atypical patterns are the result of other factors such as artifacts secondary to the methods of preparation.

GENETICS OF THE HUMAN HEMOGLOBINS

Evidence obtained from the study of many family groups suggests that the human hemoglobin types,

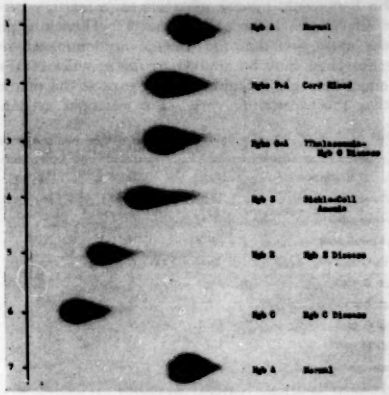


FIGURE 4. *Paper Electrophoresis of Human Hemoglobins, Showing the Actual Run of Several Naturally Occurring Hemoglobin Mixtures, Including Examples of the Known Homozygous Hemoglobin Diseases (Hgb G Specimen Provided through the Courtesy of H. Schwartz).*

with the exception of Hgb F, are controlled by a single set of allelomorphic genes.[86,89-96] These genetic fac-

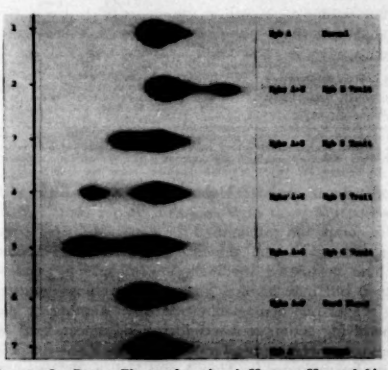


FIGURE 5. *Paper Electrophoresis of Human Hemoglobins, Showing the Actual Run of Specimens from Persons with the Heterozygous Hemoglobin-Trait Syndromes (Hgb H Specimen Provided through the Courtesy of D. Rucknagel).*

tors appear to be inherited according to mendelian laws and manifest themselves, whether in the homozygous or heterozygous state, by demonstrable changes in the hemoglobin pattern of the individual.[97] Al-

though these genetic abnormalities may have arisen as spontaneous mutations it is doubtful whether such a mechanism is responsible for the high incidence of the abnormal hemoglobins in some areas, an assumption that would involve mutation rates far in excess of any known to occur in man.[98-101] There are no data to suggest that the concept of dominance or recessiveness may be applied to the genetics of the human hemoglobins, although the expressivity of the genes must certainly vary. For example, a person heterozygous for Hgb S may have as little as 5 per cent[102] or as high as 70 or 80 per cent[103-106] of this compound rather than the expected 50 per cent, depending on the presence of modifying factors. These postulated modifiers are imperfectly understood but may involve, among other things, mutual effects of one hemoglobin type upon another or the modifying action of a second genetic defect, such as the factor responsible for thalassemia. Thus, in persons heterozygous for Hgb A and Hgb S, the amount of the latter compound is usually significantly less than the theoretical value of 50 per cent.[107,108] Furthermore, as Singer and others have pointed out, the factor for thalassemia seems to increase the expressivity of a single gene for Hgbs S, C or E so that quantities as high as 80 per cent of these abnormal hemoglobins, rather than 50 per cent, may be present.[5,89,105,109]

From a review of the percentages of the various hemoglobins found in the syndromes to be discussed it appears that the gene for Hgb A has a greater expressivity or penetrance than that of any other hemoglobin type. Consequently, Hgb A, in combination with an abnormal hemoglobin, forms over 50 per cent of the total hemoglobin mass (Table 3). When Hgb S and Hgb C are both present in the same person, each appears to have approximately the same degree of expressivity, although the latter pigment is usually found in slightly higher concentrations.[5,10,77,105,110] An evaluation of the relative effect of Hgb S versus Hgb D cannot be made at present because of insufficient data. These broad speculative considerations may also be extended to the thalassemia syndromes. The hereditary basis for this disease involves one or more sets of allelomorphic genes that are believed to be located either on different chromosomes or on the same chromosome at a point far removed from those which determine the human hemoglobins.[111,112] In support of this hypothesis is the observation that the offspring of a person with thalassemia-Hgb S disease may be normal or may inherit the gene for thalassemia, Hgb S, or both abnormalities from one parent.[112] The gene or genes for thalassemia seem to increase the expressivity of the gene for an abnormal hemoglobin so that, when Hgb S, C or E is found in

TABLE 3. *Percentages of the Human Hemoglobins in Various Hematologic Syndromes.**

CONDITION	HGB A	HGB F	HGB S	HGB C	HGB D	HGB E	HGB G	HGB H
Normal newborn	15-45	55-85	—	—	—	—	—	—
Normal adult	99+	1.0	—	—	—	—	— ?	—
Sickle-cell trait	54-78	N	22-46	—	—	—	—	—
Hgb C trait	56-72	N	—	28-44	—	—	—	—
Hgb D trait	51-65	N	—	—	35-49	—	—	—
Hgb E trait	3+	N	—	—	—	+	—	—
Hgb G trait	65	N	—	—	—	—	35	—
Hgb H trait	3+	N	—	—	—	—	—	+
Homozygous Hgb S	—	N-40	60-100	—	—	—	—	—
Homozygous Hgb C	—	N-7	—	93-100	—	—	—	—
Homozygous Hgb E	—	N-9	—	—	—	92-100	—	—
Sickle cell-Hgb C	—	N-7	35-63	37-60	—	—	—	—
Sickle cell-Hgb D	—	?	+ +	—	+ +	—	—	—
Sickle cell-Hgb G	—	N	+ +	—	—	—	+	—
Thalassemia major	10-90	10-90	—	—	—	—	—	—
Thalassemia trait	100	N	—	—	—	—	—	—
Thalassemia-Hgb S	0-20	N-20	60-88	—	—	—	—	—
Thalassemia-Hgb C	+	N-?	—	+	—	—	—	—
Thalassemia-Hgb E	?	20-40	—	—	—	60-80	—	—
Thalassemia-Hgb G	+	N	—	—	—	—	+ + +	—
Hereditary spherocytosis	80-100	N-20	—	—	—	—	—	—
Hereditary spherocytosis-Hgb S	+	?	+	—	—	—	—	—

*Values listed represent extreme ranges reported in literature. — indicates absence of compound; ? indicates no information; + & + + + refer to relative concentrations where no figures are available; Hgb F believed to be present in all persons in trace amounts; except when abnormally elevated, it is listed as N, & this amount is not deducted from other hemoglobins.

combination with thalassemia, 60 to 80 percent of the hemoglobin is in the form of the abnormal pigment.[89,103-105]

Hgb F, in contrast to the other hemoglobins, appears to be under the control of an independent set of allelic genes.[89-91] Whenever Hgb A is present in adults, the embryonic pigment is found in trace amounts. One can only speculate whether there is a direct modifying or suppressive action of a gene for Hgb A upon that of Hgb F, or whether competition for common metabolites is strongly in favor of Hgb A. Furthermore, it is possible to grade the hemoglobins in a very rough manner according to the amount of Hgb F that may be associated with them. By such a scheme Hgb A is the strongest inhibitor of Hgb F. Hgbs C, D and E are somewhat less potent in this regard, and values of up to 6 or 8 per cent of Hgb F are seen in their respective homozygous syndromes. Hgb S is the least powerful agent, and values of up to 40 percent of Hgb F may be found in homozygous Hgb S disease. With combinations of hemoglobins the degree of suppression of Hgb F production seems to be determined by the most potent inhibitor present. For example, when Hgb S, C, D or E is combined with Hgb A, the powerful inhibiting effect of Hgb A determines the trace amount of the embryonic pigment (Table 3).

Just as increased percentages of Hgbs S, C and E are found in certain thalassemia syndromes the data suggest that Hgb F production is also stimulated by the presence of the gene for thalassemia.[20,73,89,105,113] Indeed, it may be that the thalassemia gene is at the same locus as the gene for Hgb F and thereby replaces a normal fetal-hemoglobin mechanism by an abnormal one. The homozygous condition for thalassemia (Cooley's anemia) is characterized by up to 90 per cent of Hgb F.[20,30,73,114] Thalassemia in combination with mild inhibitors of Hgb F — that is, Hgbs S, C and E — results in values of 10 to 40 per cent of the fetal pigment.[57,58,103-105,109,111,115] Thalassemia in its heterozygous form with Hgb A, the most potent inhibitor of Hgb F, is characterized by normal or only slightly abnormal amounts of the fetal compound.[20]

There is suggestive evidence, therefore, that the interplay of modifying phenomena, of inhibiting and enhancing factors, may be responsible for the quantitative aspects of the hemoglobins in the various hemoglobin syndromes. Many more data, however, will be required before these postulates may be regarded as being founded on more than mere speculation. As a working hypothesis, however, the above suggestions may be summarized as follows:

Hgb A appears to have a greater expressivity than the other hemoglobin types. Hgb C may be slightly dominant over Hgb S. All the hemoglobin types appear to inhibit the expressivity of Hgb F in varying degrees — Hgb A to the greatest extent, Hgbs C, D and E somewhat less so, and Hgb S least of all. The degree of suppression of Hgb F production seems to be determined by the most potent inhibitor of the combination. The thalassemia factor, on the other hand, is associated with increased expressivity of Hgbs S, C, E and F and may, in turn, inhibit normal adult-hemoglobin formation.

(To be continued)

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MEDICAL INTELLIGENCE

ACUTE DISSECTING AORTIC ANEURYSM*

Treatment by Fenestration of the Internal Wall of the Aneurysm

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DISSECTING aneurysm of the aorta is a well described clinical and pathological entity, and yet nearly all the considerable literature on this disease is descriptive and analytical, with very little discussion of therapy. There is an incentive to attempts at surgical treatment of this disorder since it is mechanical and since the results of nonspecific treatment are poor.

Gurin et al.,[1] in 1935, reported surgical treatment of a case of dissecting aortic aneurysm in which the presenting picture was acute arterial insufficiency in one leg. Excision of the internal wall of the aneurysm at the furthermost point of its advance in the iliac artery allowed the aneurysm to bleed back into the true lumen and thus restored circulation to the extremity. The patient died of uremia on the seventh postoperative day.

Levinson, Edmeades and Griffith,[2] in 1950, recommended this operative approach for the relief of arterial obstruction due to dissecting aneurysm and suggested that it might prolong life and result in a greater percentage of "chronic or healed" dissecting aneurysms. However, the case referred to above[1] constitutes the only report of such an operation that could be found.

Johns[3] recently described closure by suture of a ruptured dissecting aneurysm of the abdominal aorta. This case was atypical in that the primary endothelial tear was in the abdominal rather than the ascending aorta. This patient also died a few days later with renal failure.

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The following case of dissecting aneurysm is worthy of report because of the observations it provides on the living pathology and because the surgical procedure performed, similar to that reported by Gurin, Bulmer and Derby,[1] accomplished a considerable reversal of the functional defect.

CASE REPORT

A 51-year-old businessman (M.G.H. 869543) felt a sudden, squeezing substernal pain, burst into perspiration and collapsed while addressing a group. Half an hour later paralysis and anesthesia of both lower extremities appeared. He arrived in the Emergency Ward about 1 hour after the onset of the illness.

Two years previously he had been examined by a physician because of a fainting spell. No abnormality was found. The blood pressure at that time was 130/60, and the pulse 56. Otherwise he had been well until the present illness.

Physical examination showed an alert man whose color was ashen and who complained of substernal oppression and pain in the middle part of the back. All pulses were present and symmetrical above the waist, but no pulse was palpable in the abdominal aorta or below. Both legs were paralyzed, cold and pale, with a level of temperature demarcation at the costal margins and of anesthesia at the groin creases.

The pulse was 44 and regular, and the respirations 18. The blood pressure was 220/90 in both arms.

The bladder contained only 5 cc. of urine, with 5 to 15 red cells per high-power field in the sediment.

Electrocardiography revealed no abnormality.

A diagnosis of dissecting aortic aneurysm was made, and it was decided to attempt surgical relief of the aortic obstruction by fenestration of the internal wall of the aneurysm.

Under Pentothal-Anectine anesthesia the abdominal aorta and iliac arteries were exposed transperitoneally. The right side of the abdominal aorta and the right iliac artery were dark purple. To the left of the midline the vessels appeared normal. There was an abrupt change in color at the midline. No pulsations were palpable in the iliac arteries or in the aorta below the level of the celiac axis. A longitudinal incision was made into the aneurysm in the lower abdominal aorta after this vessel had been mobilized. The aneurysm contained soft clot. Free bleeding was obtained from the aneurysm only after it was milked free of clot from the level of the diaphragm down. The lumen of the aorta was then opened and a piece of internal aneurysm wall, 2.0 by 2.5 cm., was excised. The true aortic lumen contained no clot and bled well from above after the extraction of thrombus from the aneurysm. The right iliac artery was thrombosed and flushed out retrogradely by injection of saline solution through the right femoral artery. Clot was also evacuated from the extension of the aneurysm down the right iliac artery. The plane of the dissecting aneurysm below the aortotomy was then closed with interrupted mattress sutures. The status of the aorta before and after operation is shown in Figure 1. After closure of the aortotomy there were excellent pulsations in the aorta and in the iliac, femoral and popliteal arteries. The pedal pulses were present on the left but absent on the right.

Circulation was restored in the abdominal aorta approximately 5 hours after the onset of the illness. Four hours after operation the right leg appeared nonviable from the mid-calf downward. Under light Pentothal anesthesia thrombus was removed from the right popliteal and tibial arteries through

a popliteal arterotomy by retrograde flushing with saline solution from the posterior tibial artery at the ankle. After this the right foot was warm, and a faint dorsal pedal pulse was palpated.

Postoperatively, the patient regained normal sensory and motor function in his legs and was alert and comfortable. Urinary output ranged from 50 to 100 cc. a day. Fluid intake was restricted to that required to cover losses. Food was limited to sugars. He was given ion-exchange resin to control serum potassium levels.

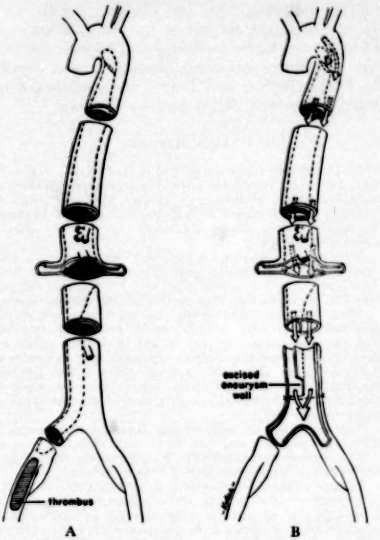

FIGURE 1. *Status of the Aorta before* (A) *and after the Fenestration Operation* (B).

The course was one of increasing uremia and neuromuscular irritability. He was given Dilantin on the 7th postoperative day, but 2 days later he died during his 1st convulsion.

At autopsy the dissecting aneurysm was found to have originated at a 1-2 cm. transverse tear 10 cm. beyond the aortic ring and to extend from 2 cm. beyond the coronary ostia to the right iliac artery (Fig. 1). The aneurysm and the true aortic lumen were patent, giving a double-barreled aorta. There was heavy thrombus lining the thoracic portion of the aneurysm, but from just above the celiac axis downward there was only a thin layer of fibrin and the window in the aneurysm wall had remained open. There was no sign of external rupture of the aneurysm. The renal arteries were open and unthrombosed although the right renal artery was slightly narrowed at its origin by a thrombosed portion of the aneurysm, which had dissected down it for a distance of 2.5 cm.

There was an area of frank infarction in the lower pole of the right kidney surrounded by considerable hemorrhage. The remainder of the right kidney was edematous, with extensive degeneration of the tubules and swelling of the endothelial and epithelial cells of the glomeruli. The left kidney showed almost uniform degeneration of tubules, with cloudy swelling. Hemoglobin casts and red cells were seen in some collecting systems. The glomeruli demonstrated a lesser degree of degeneration. The renal lesion was considered by the pathologist to be a reversible ischemic injury. Additional findings were pulmonary edema and congestion, a small pulmonary infarct on the left and a thrombus incompletely occluding the left anterior descending coronary artery.

DISCUSSION

At present there is no specific treatment for dissecting aortic aneurysms. When the disease is recognized, rest and general supportive measures are carried out in the hope that the aneurysm will spontaneously stabilize and the patient will recover. The mortality of an acute dissection is estimated variously from 75 to 90 per cent.[2,4,5] Death is usually caused by rupture of the aneurysm in the thorax.

In approximately 10 to 25 per cent of cases the aneurysm ruptures back into the lumen farther down the aorta, forming a double-barreled aorta, and the patient survives. Such chronic dissecting aneurysms are consistent with survival for many years although they will later dilate and behave much as any fusiform arteriosclerotic aneurysm.

The surgery in the case presented above was based on the natural pathologic evolution in chronic dissecting aneurysms. Relief of obstruction in the distal arteries was accomplished as in the previously mentioned case of Gurin et al.[1] Evacuation of clot from the aneurysm and decompression by fenestration reduced the encroachment of the aneurysm on the true aortic lumen and allowed blood to flow again through the normal channel as well as through the aneurysm. In this manner renal circulation was restored.

There is reason to believe that such a distal decompression of a dissecting aneurysm would reduce the mortality even through death usually results from rupture in the proximal aorta. A significant degree of aortic obstruction will accompany any long-dissecting aneurysm although obstruction may not always be complete as in this case. Aortic obstruction of this sort will result in hypertension proximal and hypotension distal to the obstruction. The frequency of hypertension on admission despite a clinical appearance of shock, noted by Levinson, Edmeades and Griffith,[2] may be better explained by this mechanism than by pre-existent chronic hypertension. Rupture of the weakened proximal aorta would be encouraged by this acute hypertension. Conversely, rupture would be less likely if the blood pressure in this vessel were reduced by surgical construction of a double-barreled aorta and relief of the obstruction.

The reported case fits this hypothesis. The blood pressure was normal before the illness. The systolic hypertension observed on admission was consistent with aortic obstruction leading to a diminished arterial reservoir. The bradycardia is explicable on the basis of carotid-sinus stimulation. After surgical relief of aortic obstruction, the blood pressure fell to

and remained at approximately 150 systolic, 80 diastolic, and the aneurysm did not rupture.

If this patient had weathered the uremia he would have had the same prognosis as a patient with a spontaneously stabilized dissection. There is reason to believe that other patients similarly treated in the future will survive.

The ideal mechanical solution to the problem of dissecting aneurysm would involve repair of the primary tear in the proximal aorta as well as evacuation of blood and thrombus from the lumen of the aneurysm. The problems of locating the tear and controlling bleeding during the repair would be formidable since the process usually starts in the region of or proximal to the great vessels of the arch. These problems may be solved by the development of safe technics of hypothermia and total circulatory arrest. It is at least certain that the establishment of a clinical diagnosis of dissecting aneurysm is passing from the academic to the practical.

Summary

A case of dissecting aortic aneurysm with total obstruction of the aorta above the level of the renal arteries is reported. Aortic obstruction was relieved by evacuation of clot from the aneurysm, fenestration of the internal wall of the aneurysm in the abdominal aorta, with establishment of a double-barreled aorta, and repair of the dissection distally.

The patient died in uremia on the ninth postoperative day without recurrence of arterial obstruction.

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BY THE LONDON POST

Diabetes Congress — Teddy Boys

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THE second International Congress of the International Diabetes Federation, held in Cambridge, England, in July, was well attended by representatives from the United States and Canada as well as by those from Europe. It was a great pleasure to everyone that Dr. Elliott P. Joslin had made the journey from Boston to deliver the ninth Banting Memorial Lecture of the British Diabetic Association as the opening lecture of the Congress. His enthusiasm and vigor were an inspiration to everyone present. Taking diabetes for the diabetic as his subject, he urged diabetic patients to be thankful that the discovery of insulin had given them the chance to live. It was their duty to live as long as possible, and he believed that strict adherence to the prescribed regimen was the best way of avoiding diabetic complications. He hoped that as far as diabetes was concerned there would never be a fund for the disease. Diabetes was a challenge, and the patients should learn to be responsible for themselves.

Professor Charles Best, F.R.S., reviewed the outstanding problems in diabetes, which he considered to revolve around the mode of insulin action. He hoped that the recent progress made in the studies on the chemistry of insulin had brought a little nearer the possibility of synthesizing the hormone and that this might perhaps eventually be in a form that would be assimilable by mouth. The topics at subsequent sessions ranged from the social implications of diabetes to the latest views on the place of hypophysectomy in patients with diabetic vascular disease.

In a meeting of academic folk, however, the agenda is never the most important thing. It provides the excuse, but what matters more is the mere meeting and the friendships that result from it. Commenting on the value of such gatherings, the *Times* recalls that in the Middle Ages it was easy and natural for a man like the surgeon Lanfranc of Milan (d.1315) to study and teach in Bologna, Pavia and Normandy before arriving at Canterbury. In later centuries the interchange of views by means of trips abroad was routine in the lives of scholars. The easy movement within the European Studium was killed by the rise of nationalism. Since the last war, however, a new era of conferences has dawned, bringing renewed opportunities for the formal and informal interchange of academic views and for the personal contact between representatives of many countries.

In Cambridge last month there was no lack of opportunity for the informal meeting. Those present will long remember the glorious weather in which the tall spires, the College buildings and the river Cam looked at their best. They will remember, too, the dinner held in the Hall of Trinity College and the charming way in which Lord Adrian, O.M., F.R.S., the master of the College, mingled with the guests from all over the world as he entertained them in the beautiful rooms of the Master's Lodge.

If such meetings as this were really common in the Middle Ages here is one respect in which the call should be "Back to the Middle Ages."

* * *

Psychiatrists, social workers and those concerned with juvenile courts have been trying to determine the etiology of what has become known as the Edwardian cult and has captured the teenager in work-

ing-class districts for the last two years. Characteristically, the Teddy boys are seen in groups at street corners at the end of the day. Black suits with velvet collars, immaculate white shirts, tight, dark trousers ("drain pipes") and smart shoes and socks are the outstanding feature of the dress. The elaborate hair style culminates in two breaking waves on the nape of the neck and involves the use of driers and hair nets.

Although it would be a mistake to imagine that the Edwardian suit is merely the uniform of a young gangster the Teddy boys of the street corners in outlandish clothes and long hair look more than a little menacing — and they quite often intend to. Clasp knives, sheath knives and bicycle chains are often carried and prominently displayed. These youths have frequently been responsible for outbursts of hooliganism and have occasionally been involved in crimes with violence. The majority of the Teddy boys, however, are not delinquents, and the Edwardian personality has been described as constrained or even formal. In cafés and bars frequented by the youths there is rarely noisy singing. On the contrary they sit in groups, conscious of their impeccable dress, and tend to make fun of the worst dressed member of the party. When seen at inexpensive dance halls the Edwardian youth will be seen to "creep" rather than dance; his facial expression is often dead, and his speech monosyllabic and dull.

Various theories have been put forward to explain the development of this cult. First of all, it is probably true that the adolescent gang-forming habit is a permanent feature of contemporary society and that the Edwardian cult is merely the current expression of this feature. In fact, it is the method that the present generations of working-class adolescents have adopted to supply the security that they seek. It offers them a world of their own, intermediate between that of the child and that of the adult, and by so doing it has re-emphasized the separateness of adolescents and so increased their tendency to quarrel with the rest of society.

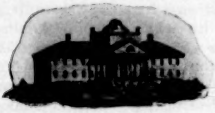
Dr. J. MacAlister Brew, writing in the *Family Doctor* takes a different view. She is training officer to the National Association of Mixed Clubs and believes that Edwardian suits are the outcome of the increasing ratio of males to females. After World War I there was a surplus of women, and to guarantee pursuit, the girls took great care in their adornment, whereas the young men were only required to be clean, personable and manly. Now, the situation has changed, and in the marriageable age group the sexes are almost equal and the tendency is for the proportion of males to increase. Because of this Dr. Brew maintains that the emphasis on personal adornment has passed to the male, finding expression at the adolescent level in terms of the Edwardian suit.

Whatever the real explanation of the Edwardian cult, it is a most remarkable current expression of adolescence. Because of the reputation that the Teddy boys have gained for being involved in outbursts of hooliganism and violence the reaction of society has been quick and hostile. Only social workers, tailors, barbers and intellectuals have a good word to say for them. Possibly because of this, the South London metropolis of the Edwardian cult has already taken the lead in a change of style in dress, the black suits being replaced by light-colored Donegal or Cheviot tweeds.

It may be dangerous to dismiss the phenomenon too lightly, for it is perhaps a challenge to the rest of society to try and understand better the problems of the adolescent. On the other hand, by his very nature, the adolescent does not always wish to be understood: he wishes to be separate.

Correction: *Acid* should be changed to *acute* in the last line of the last paragraph on page 172 of the article by Cope and Raker entitled "Cushing's Disease," which appeared in the August 4 issue of the *Journal*.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41341

PRESENTATION OF CASE

First admission. A fifteen-year-old girl was admitted to the hospital because of recurrent attacks of "liver trouble."

Seven months before admission she entered another hospital because of a sore throat, chills, fever, and pleurisy. She was said to have had lymphadenopathy. A heterophil agglutination test was positive in a dilution of 1:28, and several blood "counts" were said to have been characteristic of infectious mononucleosis. She was somewhat jaundiced and passed slightly dark urine. The icteric index was 15 units. After a few weeks in the hospital she was discharged though still slightly jaundiced. Three months later she was sent home from boarding school because of severe fatigue, low-grade fever and jaundice. Her physician was able to feel a tender liver edge 1 fingerbreadth below the right costal margin. There was no palpable splenomegaly or lymphadenopathy, however. The icteric index was 20 units, and the cephalin flocculation was ++ to +++. The stools were brown, and the urine was free of bile. She was treated with rest and a high-carbohydrate, high-protein diet. A month or so later she returned to school, but after three weeks was sent home again because of a low-grade fever, vague abdominal cramps, "grippe" and apparently an increase in jaundice. The liver was still enlarged and more tender than before. The icteric index was 14 units. The patient was referred to this hospital for further study.

The past history revealed no transfusion, vaccination or general anesthesia within the previous year, and no known exposure to hepatitis or to hepatotoxins. One brother had had jaundice four years previously.

Physical examination revealed a tanned girl who looked "the picture of health." The only positive findings were questionable scleral icterus, a palpable tender liver edge 2 fingerbreadths below the right costal margin on deep inspiration and a spleen tip felt 2 fingerbreadths below the left costal margin. Several lymph nodes, up to 5 mm. in diameter, were palpable in the neck.

The temperature was 100.4°F. The blood pressure was 120 systolic, 80 diastolic.

The urine was cloudy and acid, had a specific gravity of 1.024 and gave negative tests for bile, albumin, sugar and diacetic acid; the sediment contained 2 white cells and 12 epithelial cells per high-power field. Two two-hour urinary urobilinogen levels were 0.4 and 0.37 Ehrlich units. Examination of the blood revealed a hemoglobin of 13.2 gm. per 100 cc., a hematocrit of 41 per cent, a red-cell count of 4,490,000 and a white-cell count of 8300, with 56 per cent neutrophils, 35 per cent lymphocytes, 5 per cent monocytes, 3 per cent eosinophils and 1 per cent basophils. The red cells appeared normal except for occasional stippling. The reticulocyte count was 1.1 per cent. The sedimentation rate was 0.2 mm. per minute. The bromsulfalein retention was 7 per cent forty-five minutes after injection. The albumin was 5.28 gm., the globulin 1.87 gm., the nonprotein nitrogen 28 mg., the fasting blood sugar 80 mg., and the bilirubin 1.9 mg. direct and 2.7 mg. total per 100 cc. The serum iron was 330 microgm. per 100 cc. (normal, 125 to 200 microgm. per 100 cc.). The prothrombin time was 21 seconds (normal, 17 seconds). Cephalin flocculation was + in twenty-four and ++ in forty-eight hours. Thymol flocculation was negative. Thymol turbidity was 0 units per 100 cc. Heterophil and brucella agglutination tests were negative. An x-ray film of the chest was normal. A Graham test after oral ingestion of dye showed no contrast medium in the gall bladder. A considerable quantity of dye remained in the stomach. No opaque stones were seen. The patient was discharged without a definite diagnosis on the ninth hospital day to follow a regimen of moderate rest and an adequate, but not rigid diet.

Second admission (three and a half years later). Two months after discharge the patient returned for a checkup, although she had been asymptomatic and had felt unusually well. On physical examination small cervical lymph nodes were palpable, but there was no other lymphadenopathy. The spleen and liver could not be felt now, and there was no tenderness in the region of the liver. The bromsulfalein test showed 5 per cent retention in the serum in forty-five minutes. Cephalin flocculation was + in forty-eight hours. The serum bilirubin was 1.6 mg. per 100 cc. direct and 2.4 mg. total; serum iron was 220 microgm. per 100 cc. Five weeks later the serum bilirubin was unchanged, bromsulfalein retention was 8.8 per cent, cephalin flocculation was normal, the alkaline phosphatase was 2.7 units per 100 cc., and the urinary urobilinogen was 0.7 Ehrlich units in two hours.

When the patient was seen again, seven months later, she had been asymptomatic except for the appearance of scleral icterus on two occasions: on the third and fourth days after a knee arthrotomy at another hospital, and during an attack of "grippe."

The serum bilirubin was now 1.2 mg. direct and 1.8 mg. total per 100 cc. Cephalin flocculation was + in twenty-four and +++ in forty-eight hours.

Fourteen months before admission the patient was operated on at another hospital for acute pain in the right lower quadrant of the abdomen, accompanied by local tenderness and associated with leukocytosis. At operation the appendix was not obviously inflamed, and the surgeon believed that there was an "acute mesenteric adenitis." Two days after operation jaundice appeared, and then gradually receded. The icteric index reached 16 units; cephalin flocculation and thymol turbidity were normal. The patient was asymptomatic postoperatively. One week after operation physical examination was negative except for icterus and a barely palpable, minimally tender liver edge. The total serum bilirubin was now 2.5 mg. per 100 cc.

The patient remained well for about a year and then entered the hospital because of intermittent jaundice and fatigue. The episodes of jaundice usually lasted about two days and were accompanied by dark urine. Physical examination was unchanged. The total serum bilirubin was 4.1 mg. per 100 cc.; bromsulfalein retention was 6.2 per cent. Other laboratory findings were normal.

A liver biopsy was performed.

Differential Diagnosis

Dr. Sydney S. Gellis*: I am dealing with a patient who had an acute febrile illness associated with jaundice about four years before the last admission. She was well for the four years except for repeated episodes of low-grade obstructive jaundice and fatigue.

At the time of admission to the other hospital, seven months before the first admission to this hospital, the symptoms and findings were consistent with infectious mononucleosis except for the heterophil-antibody agglutination, which cannot be considered positive. In a high percentage of patients with infectious mononucleosis the liver may become enlarged, and jaundice of an obstructive type may develop as a result of the diffuse involvement of the liver. Pulmonary findings are certainly not rare. The heterophil agglutination may have been low because the blood was drawn too early or too late in the course of the disease, but no further information about that is given.

Tuberculosis, with subsequent spread to the liver, could produce both the pulmonary and hepatic signs. Diffuse tuberculosis, with minimal involvement of the lungs and gastrointestinal tract, has been reported. I shall eliminate this disease because the patient's nutrition continued to be excellent.

Leptospirosis may begin suddenly with sore throat, chills and pulmonary signs and finally cause jaundice. It would be most unusual for a patient who recovered from mild disease of this sort to continue to have chronic liver disease.

Amebic hepatitis, in which the lungs may become secondarily involved, must also be considered. The fact that diarrhea is frequently absent in patients with amebic hepatitis helps to obscure the diagnosis. Pain in the chest is a frequent symptom as a result of either direct extension of the abscess to the lung or irritation of the diaphragmatic pleura. In the latter case, the pain is pleuritic and is more common with an abscess than with the diffuse form of amebic hepatitis. X-ray films of the chest usually reveal a triangular elevation of the right leaf of the diaphragm, with abscess, and blunting of the costophrenic angle as a result of pleural effusion, with the diffuse type of amebic hepatitis. It would be helpful to know whether the pleurisy was right-sided, for if it were, I should seriously consider this possibility. Chills and septic fever occur regularly in amebic hepatitis, and jaundice when it does occur is relatively mild. The patient had no liver enlargement, which argues against this diagnosis, nor did she have abdominal pain, which is perhaps the commonest symptom of amebic hepatitis. Finally, patients with this disease are much more ill than the patient under discussion was, so I shall discard amebic hepatitis.

The history fits perfectly with the syndrome called, among other names, constitutional hepatic dysfunction, with which patients are well except for intermittent bouts of jaundice, with or without fatigue. Against this condition is the elevation of the direct bilirubin, which indicates an obstructive type of jaundice. In this syndrome the elevation is in the indirect bilirubin.

I think that I can eliminate malignant tumors of the liver because the patient's nutrition was good, but I cannot eliminate benign tumors, although the acute febrile illness makes them unlikely. A choledochal cyst may cause intermittent jaundice. As tension builds up in the cyst it blocks drainage from the bile ducts and produces jaundice. Then the cyst empties itself, and jaundice disappears. No one reported palpating a tumor, but in some patients it may not be felt. Although I cannot easily eliminate this diagnosis I do not believe it fits in well with the early acute febrile illness.

I shall eliminate all types of hemolytic anemias because the jaundice was obstructive and not hemolytic. The serum iron of 330 microgm. per 100 cc. is not helpful since it may be increased in any diffuse liver disease, the mechanism of this being poorly understood. The increase does not seem to be that seen in hemolytic anemia with jaundice, nor were the reticulocyte count, the red-cell count and the hemoglobin in keeping with such a diagnosis.

On the same basis I have already eliminated constitutional hepatic dysfunction, which may be confused with nonspherocytic hemolytic anemia, in which it may be difficult to demonstrate hemolysis. In constitutional hepatic dysfunction the bilirubin increase is in the indirect fraction. Dubin and Johnson[1] de-

*Pediatrician-in-chief, Beth Israel Hospital.

scribed a syndrome in which the liver appears unable to handle bile pigment and direct bilirubin becomes elevated. I think I can eliminate that disease because the bromsulfalein retention was not abnormally elevated and flocculation tests were positive on occasions.

Now I have to cope with the whole file of causes of obstructive jaundice. Gall-bladder disease in the form of infection is uncommon in this age group although it has been reported. At no time was marked tenderness over the gall bladder reported, and no biliary colic was mentioned. The one attack of pain does not sound as though it originated in the gall bladder although I cannot be certain of that. The history was certainly suggestive of appendicitis, for the pain was in the right lower quadrant. I tend to shy away from the gall bladder as an explanation of that attack.

The gall bladder did not fill, although two attempts to fill it were made. There are several reasons why the gall bladder may not have filled. It may have been absent. There may have been hydrops of the gall bladder. Stones that were nonopaque and did not show in the films may have filled the gall bladder so completely that no dye entered it. There may have been an open sphincter from the gall bladder, which prevented concentration of the dye. Diffuse liver disease, of course, is a handicap for a good Graham test. Perhaps there was an initial acute attack of cholecystitis, with some jaundice, that subsided but left the cystic duct edematous. Perhaps from time to time the edema became more marked and thus blocked off the excretion of bile. I cannot eliminate cholecystitis though I do not care for the diagnosis.

I know that a liver biopsy, which I am not told was positive, was done. I assume that it was a needle biopsy and if so that Dr. Castleman is prepared on this basis to give a definite diagnosis. I do not believe that he will dare show microscopical sections that merely suggest obstruction without revealing its cause. On this very very flimsy basis, which I suspect is unfair medically speaking, together with an inconclusive clinical history, I shall abandon the diagnosis of cholecystitis or cholelithiasis or both.

At this point I have with ease eliminated about every diagnosis. I am left, for better or for worse, with an acute infectious process that began about four years earlier. The acute febrile onset, the sore throat, the pleurisy and so on are in favor of an infectious process. This process resulted in damage to the liver, chronic impairment of liver function, the tenderness of the liver noted on several occasions, jaundice and fatigue. What kind of infection could have been responsible? I have already mentioned and eliminated tuberculosis, Weil's disease and amebic hepatitis. I shall throw out syphilis because during so many hospitalizations a positive serologic test and other stigmas suggestive of the disease should have been noted. Brucellosis and malaria do not fit with the signs and symptoms. I am left, therefore, with a viral hepatitis. This could have been an infectious-hepatitis virus, a homologous-serum-hepatitis virus, although there was no history for it, or the virus of infectious mononucleosis although I have given my arguments against the last agent. I hope that Dr. Castleman found viral hepatitis in the biopsy, with perhaps moderate increase in fibrous tissue.

What arguments can I raise against my own diagnosis? The number of patients whose sole indication of damage from viral hepatitis is a mild elevation of direct bilirubin are relatively few. This patient had suggestive changes from time to time, none of which were exciting. Most patients show abnormalities in additional functions of the liver, such as positive flocculation tests. However, in children, and I specify children, with posthepatitic cirrhosis, positive tests may appear only late in the course of the disease. Against infectious hepatitis occurring at the time of the initial acute illness is the fact that when it occurs within a family the other children in the family have a high incidence of hepatitis that is not recognized clinically because of the absence of jaundice.

It is obvious that I am disturbed with this case. I should have liked more positive findings. I should have preferred a biopsy taken at exploration to a needle biopsy. I shall stick by my guns and decide that this patient had a diffuse hepatitis, with some increase in fibrous tissue.

A PHYSICIAN: Was a stool examination for parasites made?

DR. BENJAMIN CASTLEMAN: This patient was being cared for by Dr. Chester M. Jones; I am quite sure that he examined the stool.

DR. ALLAN M. BUTLER: We might ask where the patient lived.

DR. CASTLEMAN: In New England.

DR. BUTLER: Had she traveled a great deal, or not?

DR. DANIEL S. ELLIS: I do not think so.

DR. JACOB LERMAN: I should like to raise the question of sarcoidosis.

DR. CASTLEMAN: What do you think of sarcoidosis, Dr. Gellis?

DR. GELLIS: Not much.

DR. ELLIS: Dr. Gellis, you stressed the bilirubin and the part the direct and indirect fractions play in the differentiation between obstructive and nonobstructive jaundice. I assume that when you spoke of the elevation of the direct fraction as indicating obstruction you included intrahepatic as well as extrahepatic obstruction of the biliary tree. It is my impression that the fractionation of the van den Bergh test is not a reliable guide by which one can differentiate intrahepatic and extrahepatic disease.

DR. GELLIS: That impression is correct; an elevation of the direct fraction does not distinguish between intrahepatic and extrahepatic obstruction. There was, however, no evidence from the liver-function tests or the clinical findings strongly suggesting extrahepatic obstruction. For this reason I

assume that the patient had a diffuse intrahepatic process.

Clinical Diagnosis

Chronic hepatitis.

Dr. Sidney S. Gellis's Diagnosis

Viral hepatitis.

Anatomical Diagnosis

Chronic idiopathic jaundice, with unidentified pigment in liver cells (Dubin–Johnson syndrome).

Pathological Discussion

Dr. Castleman: The biopsy was a needle biopsy, as Dr. Gellis suspected; however, it was performed on

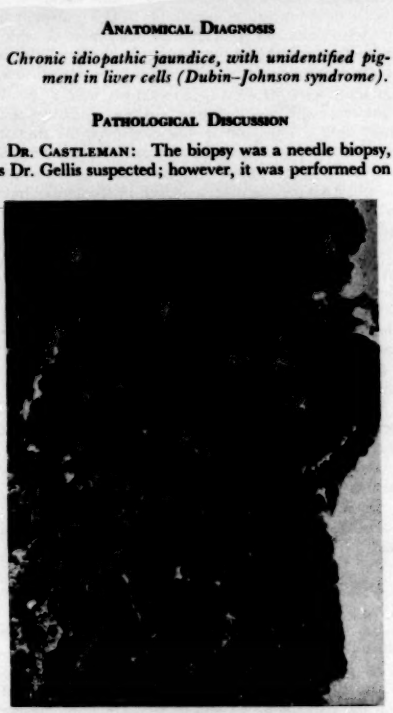


Figure 1.

the first admission four years ago. At that time Dr. Tracy B. Mallory described the liver as normal in architecture, with no evidence of inflammation. The only abnormality was the presence of clumps of golden-brown, granular pigment within most of the liver cells, but not in the Kupffer cells, bile ducts or stroma (Fig. 1). Special stains appeared to rule out hemosiderin, ceroid, hematoidin, aposiderin, lead and bismuth. A definite diagnosis was not made.

This description of Dr. Mallory corresponds exactly to the lesions in the 12 cases recently reported by Dubin and Johnson[1] from the Armed Forces Institute of Pathology called "Chronic Idiopathic Jaundice with Unidentified Pigment in Liver Cells."

I was hoping that Dr. Gellis, when he talked about the pigments in the liver cells and mentioned the paper of Dubin and Johnson, would continue on that subject. So far no one has been able to identify the pigment. It is easily seen even in unstained sections. According to Dubin and Johnson these patients have recurrent attacks of jaundice, often exacerbated by operative procedures or infections, which was true in the patient under discussion here. The condition is differentiated from the so-called constitutional hyperbilirubinemias in that these 12 patients all had a high direct bilirubin whereas those with constitutional hyperbilirubinemia have an elevation of the indirect bilirubin. These patients have positive Graham tests — that is, the gall bladders are not filled by the dyes used in cholecystography. Between attacks the patients are healthy and get along perfectly well; the prognosis is good. It is important for us, as pathologists, to realize that this pigment is not bile stasis. In many cases similar to this operations have been done, with the understanding that the patient had obstructive jaundice, because this material was mistaken for bile. The absence of any cellular infiltration rules out any form of hepatitis.

I shall read a comment from the paper of Dubin and Johnson[1]: "We are inclined to believe that the condition represents an inborn deficiency of the liver characterized by multiple defects of metabolism whereby the liver cannot properly excrete such substances as (a) bilirubin (b) the pigment which accumulates in liver cells (c) bromsulfalein and (d) dyes used in cholecystography."

A case has recently been reported from Israel.[2]

Dr. Ellis, do you have any further comments?

Dr. Ellis: You might tell us how the patient is now. I have not seen her since I did the biopsy.

Dr. Castleman: The biopsy was done on the first admission in 1951; since then, as described in the protocol, she has had attacks of jaundice four or five times. She was seen recently because of an attack of colitis, but that apparently did not produce any jaundice. It is important to tell this patient that she can go on perfectly well, without worrying about chronic hepatitis, which is what most physicians believed that she had. It was only after I heard Dubin read his paper a year or so ago and we were discussing cases with queer pigments that Dr. Ellis reminded us of this particular case.

A Physician: How high has the bilirubin been?

Dr. Castleman: The bilirubin has been as high as 6 mg. per 100 cc.

Dr. Gellis: We had a very young child with this condition whose bilirubin at one point went as high, I think, as 15 to 20 mg. per 100 cc. That case has not been reported yet. I think there is going to be considerable confusion about this condition because there are other conditions in which the metabolic defect affects the indirect rather than the direct fraction. There will have to be clarification of the dif-

ferent pigments that are being seen. I did not consider Dubin's disease likely, because I believed that the patient would have been icteric sooner. She should have had respiratory infections at an earlier age than this, which ordinarily precipitates the jaundice of Dubin's disease. I should have expected the bromsulfalein retention to be marked or at least abnormal when the bilirubin was elevated; it was 5 per cent on one occasion and 7 per cent on another, and on both occasions the direct bilirubin was elevated.

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CASE 41342

Presentation of Case

A seventy-year-old woman entered the hospital because of obstruction of the right nostril.

The patient stated that her right nostril had felt "stuffed up" for several years; however, in the four or five months before admission, the obstruction had become more severe, so that at the time of admission she was unable to inhale or exhale through the right nostril. Four months before admission her physician told her that her nose contained a bone that was three times the normal size. Treatment with a spray gave some relief. Shortly thereafter, it was noted that the patient's face appeared swollen on the right side, that the eye was constantly tearing and that the conjunctiva was injected. She was unable to wear her upper denture because of right-sided swelling of the jaw. She had lost no weight and had generally felt well. She had no difficulty breathing through the left nostril, swallowed easily and had had no headaches or change in vision. She had noticed some decrease in hearing in the left ear during the past year, but no change on the right side. She denied any recent infections, including otitis and mastoiditis. She had not noted any tenderness or swelling in the neck.

Her father's family had always been "diabetic." The patient had had known diabetes for twelve years and was currently taking 30 units of NPH insulin daily. A prescribed diet was not being followed, and she was not testing the urine specimens. Thirteen years before admission a "necrotic" gall bladder had been removed for right-upper-quadrant pain. Nine years later a vaginal hysterectomy was performed during the repair of a cystocele and rectocele. The family history revealed that 2 siblings had died of cancer, 2 of pneumonia, and 1 of tuberculosis. There were no significant cardiorespiratory, gastrointestinal or genitourinary symptoms. A port-wine "stain" had been present over the right lower portion of the back since birth.

Physical examination revealed a well developed, obese woman in no distress. Facial asymmetry was produced by a swollen right cheek and underlying maxilla. The right conjunctiva was injected, and the right fundus showed white, round, discrete exudates. Auditory acuity was decreased on the left side. The right nostril was obstructed by a moist, smooth but lobulated, green growth. Evidence of stasis dermatitis was present over both legs, and a chronic ulcer was noted over the left lateral malleolus. A port-wine mark was located over the right lower portion of the back. A movable lymph node, 1 cm. in diameter, was palpable in the left axilla. The heart,

Figure 1. *Roentgenogram, Showing Malignant Tumor of the Right Maxillary Antrum That Caused Diffuse Increased Density of the Antrum and Associated Destruction of the Lateral and Medial Walls.*
The lesion extends into the right ethmoid region.

lungs and abdomen were normal. Neurologic examination was negative.

The temperature was 97.6°F., the pulse 84, and the respirations 18. The blood pressure was 140 systolic, 90 diastolic.

Urinalysis showed occasional red cells, 5 white cells and scattered calcium oxalate crystals per high-power field in the sediment, and negative tests for albumin and sugar. Examination of the blood revealed a white-cell count of 7700, with a normal differential, and a hemoglobin of 14.6 gm. per 100 cc. On smear, the red cells and platelets were normal. The nonprotein nitrogen was 28 mg., the fasting blood sugar 172 mg., the cholesterol 298 mg., and the total protein 6.1 gm. per 100 cc. The prothrombin time was 83 per cent. A blood Hinton test was negative. X-ray films of the paranasal sinuses revealed clear frontal and sphenoid sinuses. The right maxillary and ethmoid sinuses were obscured by a homogeneous density, which had eroded through the inferolateral wall of the antrum and through the medial wall into the ethmoid area (Fig. 1). The orbital margin of the right maxillary sinus was preserved.

On the fourth hospital day a consultant observed that the right nostril was completely blocked by a

tumor mass or by the inferior turbinate deflected toward the septum. He mentioned a definite bulging of the anterior wall of the antrum and of the hard palate on the right side. On the eighth hospital day an operation was performed.

Differential Diagnosis

Dr. David Weisberger*: This seventy-year-old woman complained of obstruction of the right nostril and apparently had a deformity of the antrum. If I saw a mass protruding through the nares I should think primarily of a neoplastic process. The first neoplastic process in this age group with this amount of destruction of the wall of the antrum that I would think of is epidermoid carcinoma. The history contributes to that impression. The commonest cause of a destructive type of neoplasm in this age group is an epidermoid carcinoma.

If I were to consider the gross appearance of the tumor and believed that the green pigment was an integral part of the neoplastic process, I should have to think of rare conditions. I hate to mention chloroma in this particular case because it is so rare. I have never seen a case. Chloromas are characterized by green pigmentation and usually arise from bone marrow. There is no bone marrow in the membranous bone around the face so that is against chloroma. So is the normal blood smear and normal white-cell count, for they are usually found in patients who have had leukemia.

Dr. Austin L. Vickery: In abstracting this case I also noted the reference to the green color of this tumor, which I think was considered to be a green hue. Dr. Lurie, whose patient this woman was, made the remark about the color of the tumor. Perhaps Dr. Hanelin will show the x-ray films.

Dr. Joseph Hanelin: I cannot add anything to the description of the original films, which is excellent. There is fairly typically malignant-appearing neoplastic involvement of the right maxillary antrum (Fig. 1), indistinguishable from epidermoid carcinoma. The homogeneous density of the antrum is very clearly shown. The large mass has broken through both the infralateral and medial walls of the sinus and is projecting into the nose and invading the ethmoid region. There is some suggestion of nasopharyngeal extension in the original film.

Dr. Moses H. Lurie: I should like to ask Dr. Weisberger if he would not expect a history of bleeding from the nose with carcinoma.

Dr. Weisberger: Yes; as an early sign. We do not know whether there was such bleeding.

Dr. Lurie: There was no bleeding from the nose.

Dr. Weisberger: Of course, at the time of admission, there was a deformity.

Dr. Bernard M. Jacobson: Dr. Weisberger mentioned carcinoma as the most likely diagnosis and went on to a very rare tumor, chloroma. I wonder if he would want to consider a nasopharyngeal tumor that is not so rare — namely, a solitary plasmacytoma. Each year we see one or two cases of plasmacytoma arising in the nasopharynx.

Dr. Weisberger: I think it is a possibility. I wonder how frequently it occurs as a solitary tumor of a postmaxillary sinus. I have not seen it or heard of it. I think that in a seventy-year-old woman, one must first rule out epidermoid carcinoma, which does obstruct the nares, produces a deformity of the face and encroaches on the alveolar process. If it proved not to be epidermoid carcinoma, many other tumors could be considered possibilities. Fibrous dysplasia is one. This woman was somewhat old for fibrous dysplasia, which can produce about the same picture of destruction and homogeneous density in the antrum. A benign osteoma is another with which there may be a destructive process, but I have never seen that type of neoplasm protruding into the nares. The only reason I jumped to the rare tumor of chloroma was that I was confused about the green pigmentation. Whether that was the result of a pseudomonas infection or of neoplasm I do not know.

Dr. Lurie: When I saw the patient, I did not consider a carcinoma. I considered fibrosarcoma as my first diagnosis. On that basis, instead of trying to take a biopsy for a diagnosis, I recommended that we remove the whole tumor. A Moore operation alongside the nose was done, and the cheek was laid back; we took out the upper maxilla, leaving its roof to keep the eye in position. The mass had broken through the antrum posteriorly and extended through the surface of the sphenoid, which we also removed. It is interesting that, during the operation, the tumor did not even act like a fibrosarcoma, because there was very little bleeding from it. I may say that the patient got along well for a while.

Clinical Diagnosis

Fibrosarcoma of maxillary antrum.

Dr. David Weisberger's Diagnosis

Epidermoid carcinoma of maxillary antrum.

Anatomical Diagnosis

Multiple myeloma involving both maxillary antrums and (metacarpal bone).

Pathological Discussion

Dr. Vickery: The specimen we received consisted of several fragments of tissue, the largest of which was a 5-cm. mass of solid tumor composed of bone and fibrous tissue. Microscopical examination disclosed areas of new bone as well as fibrous tissue in which there were foci of necrosis and a considerable cellular infiltrate. The zones of necrosis in the mass were probably responsible for the green color, described clinically. The gross appearance of the tumor, its location and the presence of bone trabecu-

*Chief of Dental Service, Massachusetts General Hospital.

lae in fibrous tissue led to the diagnosis of the benign lesion of ossifying fibroma (fibrous dysplasia). We were not entirely happy about that diagnosis because Dr. Castleman noted that there was a fairly widespread infiltration of plasma cells in this tumor. The plasma cells were thought to be associated with the inflammatory reaction rather than with a myelomatous origin. Nevertheless we advised that blood serum protein studies be done. These data, including fractional serum protein determinations, did not suggest a myelomatous process.

The follow-up course of the patient gave the true answer. She was apparently quite well for about a year, and then began to complain of tearing on the left side. Eventually x-ray films of the area were taken. Dr. Hanelin will show the films taken about eight months after the original procedure.

DR. HANELIN: The later films show a mass in the nasopharynx and destruction of the hard palate, continuous with the nasopharyngeal tumor. I am not sure that there is residual disease in the right antrum. The left antrum is slightly hazy but no bone destruction is visible. Dr. Lerman, who was taking care of the patient, noticed swelling of the palm of the hand, and we were able to demonstrate a large, expansile, destructive lesion of the right second metacarpal; the bone is almost totally missing (Fig. 2). The tumor appears to extend freely into the soft tissue of the palm.

DR. VICKERY: After the lesion involving the left antrum had been found a second operative procedure, with excision of the tumor, was performed. Microscopical examination of the tumor removed from the left antrum revealed that it was very cellular, being composed principally of sheets of plasma cells. After we saw these sections we reappraised the biopsy done a year and a half previously and decided that it was the same process, but considerably masked by extensive inflammation and fibrosis. This patient's course is not uncommon for a presumably solitary plasmacytoma, which is indeed an unusual tumor. Other tumors may later develop elsewhere in the skeleton, giving the picture of multiple myeloma. In a review of 104 cases of primary plasma-cell tumors involving the upper air passages and oral cavity Stout and Kenney* found that the lesion was four times as frequent in men as in women and that three quarters of the cases developed in the fifth, sixth and seventh decades of life. About 50 per cent of these patients had metastases, of which 30 per cent were to bone and 56 per cent to lymph nodes. The authors mentioned the possibility that these so-called metastases represented examples of multiple primary involvement, in which the nasal or oral lesion merely first became evident.

DR. HANELIN: Was a biopsy of the hand done?

DR. VICKERY: No; it was not. I think that this metacarpal lesion has been considered entirely consistent with myeloma.

*Stout, A. P., and Kenney, F. R. Primary plasma-cell tumors of upper air passages and oral cavity. *Cancer* 2:261-278, 1949.

DR. HANELIN: Yes; it is, as well as with a number of other lesions. Although myeloma can involve bone anywhere, myelomatous involvement of the hands is extremely rare.

DR. JACOBSON: Was a bone-marrow puncture done?

DR. VICKERY: Dr. Lerman, do you have a comment?

DR. JACOB LERMAN: After the first operation the finding of plasma cells invading the tumor raised the possibility of myeloma. However, the urine did not contain any albumin, the total protein and albumin-globulin ratio were normal, and the calcium and phosphorus were also normal. A bone-marrow puncture was not done. At this time no other tumors were discovered.

FIGURE 2. *Roentgenogram of the Hand.*
There is an expansile, destructive lesion of the right second metacarpal that was considered to be similar in etiology to the sinus neoplasm although no histologic confirmation was obtained.

At the time of the second admission, when the lesion in the right hand was discovered, the question of multiple myeloma was again raised. When the diagnosis was established urethane and cortisone were started.

I last saw the patient two months after operation. She was free of any symptoms referable to the nose and antra; the lesion in the hand was, if anything, smaller. There were no new lesions anywhere.

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PSITTACOSIS ON THE INCREASE

EVER since 1951, when the United States Public Health Service relaxed the interstate and foreign quarantine regulations for psittacine birds,[1] there has been a great increase in the number of such birds, particularly parakeets, sold for household pets in this country. Coincidentally, the number of cases of psittacosis reported from various parts of the United States has risen considerably. Whereas a total of only about 25 to 30 cases were reported annually to the National Office of Vital Statistics for each of the years 1945 through 1951, this number increased to 135 in 1952, 169 in 1953 and 303 for the first three months of 1954.[2] In recent weeks up to 10 cases have been reported in each of the weekly issues of the Communicable Disease Summary issued by the National Office of Vital Statistics of the United States Public Health Service.

It may be assumed, however, that most cases of psittacosis are not reported either because other diagnoses, particularly primary atypical (or "viral") pneumonia, are made or because the relation to psittacine or other birds is not suspected. Of the cases that have been reported, a large proportion have been proved serologically and some by isolation of the virus; most of the patients have been exposed to sick parakeets at home or in pet shops. The states of California, Minnesota and Washington have been supplying the largest number of reports on authenticated cases in the last few months, but this may be due merely to the greater interest and awareness on the part of the physicians and health authorities in these states. Other reports have come from many states in all parts of the country; indeed, 29 states and the District of Columbia all reported cases during 1954.[3] In that year 8 states each reported more than 15 cases, Texas and California leading, with 151 and 56 cases, respectively.

The importation, breeding, sale or offer for sale of birds of the psittacosis family had been prohibited under the sanitary codes of New York City and New York State since 1938. These restrictions were revoked early in 1952 after the modification of the United States Public Health Service regulations whereby foreign quarantine of such birds was made more lenient and interstate restrictions were completely removed, except for the requirement that any shipment of psittacine birds must be accompanied by a permit from the health department of the state of destination, when required by such a department. The action of the New York State Department of Health was justified, in part, by the following considerations: the diminished importance of psittacosis as a health problem; the availability of effective curative therapy in the broad-spectrum antibiotics; the recognition of other and larger reservoirs of infection among pigeons, ducks, chickens, turkeys, canaries, sea gulls and so forth; insufficient evidence that psittacine birds are a greater hazard, or a cause of more

serious infections, than other varieties; and the practical difficulties or impossibilities of adequate enforcement of the interstate regulations.[1]

Soon after these regulations were revoked cases of psittacosis attributable to parakeets were recognized in New York State. Drachman[4] reported 2 small outbreaks in Westchester County involving 3 proved cases each in Peekskill and Ossining, and several other probable cases in these areas. The Peekskill cases occurred among employees of a chain store selling parakeets and other birds, and the Ossining episode represented a typical household outbreak. Both were traceable to parakeets placed on sale since the modification of the federal regulations and the removal of the prohibition of traffic in psittacine birds in New York City and State.

More recently, Fitz, Meiklejohn and Baum[2] presented a study of 18 cases of psittacosis in Colorado that are considered to represent an experience similar to that being encountered in many other places in this country. Fifteen of the 18 patients had been exposed to parakeets, 5 of them in pet shops and the other 10 in the home (1 of these had intimate exposure to pigeons, turkeys and chickens in addition to parakeets); 1 had a laboratory exposure to infected pigeons, 1 had been exposed to wild pheasants, and the eighteenth patient was not aware of any exposure to birds.

The clinical course and findings were characteristic. Constitutional symptoms were often quite severe, with chilliness, shaking chills and cough being experienced by most of the patients, but sputum was usually scant and none complained of pleuritic pain. The physical signs were not remarkable, fine rales being the most common auscultatory finding, and some enlargement of the spleen was made out in several cases. A scattered macular erythematous rash occurred in 1 case. White-cell counts ranged from 5500 to 11,000 in the first week but were as high as 16,000 later. No significant bacteria were demonstrated in sputum and blood cultures. Chest roentgenograms all showed infiltrations, usually ill defined and mostly in the lower lobes. The febrile course ranged from three to twenty-four days, depending on the therapy used. Treatment with each of the 3 tetracycline antibiotics was successful in 11 of the 12 patients in whom they were used and resulted in rapid clinical improvement and loss of fever. Penicillin was relatively ineffective unless given parenterally in large doses of the soluble aqueous solutions.

The diagnosis was made on the basis of a significant titer or rise in titer of complement-fixing antibodies to the psittacosis virus. Isolation of the virus from suspected parakeets was attempted in 3 cases, and was successful in each; this was carried out in the Virus and Rickettsial Section of the Communicable Disease Center at Montgomery, Alabama. Pigeons thought to be responsible in 1 case were found to have significant titers of psittacosis antibodies in their serum.* Inapparent infection was demonstrated by the finding of a complement-fixation titer of 1:16 or higher in 4 of 12 persons who shared contacts with the infected birds, either in pet shops or at home, but gave no history of illness.

The Colorado report goes on to point out that since the relaxation of federal and local controls there has been a great increase in popularity of birds as pets. One Denver chain store alone had sold nearly 9000 birds in 1953. The production of birds in this country has therefore greatly increased, and, along with this, the business of smuggling birds, especially along the southern border, has assumed massive proportions; this involves particularly birds that are being shipped in large numbers from Europe to Mexico. These smuggled birds have been badly handled and mixed with birds of Central and South American origin that are known to be carriers of the virus; the expected epizootics of psittacosis have been frequent among such birds.

Since it appears unlikely that the disease will be readily eradicated a number of suggestions are made for avoiding serious trouble. All persons acquiring birds as pets or working with them should be made aware of the risk of psittacosis, which is a real one even with birds that appear healthy but may be greater from those that are obviously ill; the danger is not eliminated by the addition of chlortetracycline to the drinking water,[6] a practice used by some dealers. Physicians should suspect psittacosis in unexplained fevers and in cases of "viral pneumonia," especially if there are severe systemic symptoms, and inquire regarding contacts with birds. Appropriate therapy, preferably with tetracycline or one of its analogues, should be used in an oral dose of 2 gm. daily or, in severe cases, 500 mg. intravenously every twelve hours. For the laboratory diagnosis, since viral isolation will probably not frequently be attempted, it is important to obtain serum as early as possible in the acute phase and again during convalescence to demonstrate a significant rise in titer. An elevated titer in a single specimen may occasionally be difficult to interpret, and in some cases a rise in antibody titer may be suppressed if successful treatment is undertaken early. This increases the importance of taking a careful history and having a high index of suspicion when there has been exposure to birds.

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*Problems in the diagnosis of psittacosis were recently discussed by Meyer.[5]

FACTS ABOUT RADIOACTIVITY

One of the great advantages in working with radioactive substances in the field of biology and medicine is that radioactivity can be detected in amounts so small as to have no perceptible effect on the biologic activities of the cell. The wide availability of delicate instruments, combined with the public interest in the major bulwark of the national security, the Atomic Energy Commission program, has resulted in much publicity about the fallout of radioactivity that follows test explosions of atomic bombs. Ease of detection of radiation and its biologic effectiveness are a long way apart. Available instruments detect radiation far below the threshold of detectable biologic effects.

Some geneticists have been concerned by the fallout from the test explosions on the thesis that all exposure to radiation is bad. With this thesis no one can quarrel, for there is no question that radiation will produce mutations and that most mutations produced are deleterious, at least by current standards. However, so much confusion has resulted from some of the more alarmist statements made that it seems worth while to call attention to a few facts that enable one to place the problem in perspective.

In the United States as of January 1, 1955, the dosage rate of radiation due to fallout from test explosions of nuclear devices was 1 mr per year. When people are crowded together, as on public conveyances, the naturally radioactive materials in their bodies (mostly radioactive isotopes of potassium and carbon and minute traces of radium) give them radiation at twice this rate, or 2 mr per year. The farmer who walks over ground on which he has spread commercial phosphate rock fertilizer receives radiation at a rate of over 200 mr per year from the fertilizer. The person who wears a luminous-dial wristwatch irradiates much of his body, including his gonads, at an average rate of 40 to 50 mr per year. Entirely apart from these conceivably avoidable sources of radiation, a hermit on a Cape Cod sandspit would receive cosmic-ray radiation at a level of between 30 and 40 mr per year; an inhabitant of Colorado would receive perhaps twice as much. The average human being gets a dose of somewhat under 30 mr per year from his own radioactivity. If he picks the most favorable habitation from the standpoint of cosmic radiation he gets about the same amount of radiation from that source; if he spends much time in crowds he receives additional radiation at the rate of 2 mr per year, and if he wears a wristwatch he adds 40 mr per year to this.

There are appreciable variations in the dosage of natural radioactivity derived from the soil, the highest perhaps being in regions rich either in uranium or in phosphate rock. On clay soil near sea level the total radiation from cosmic rays and the naturally occurring radiation in the soil is at the rate of between 90 and 100 mr per year.*

*Sievert, R. M., and Hultqvist, B. Variations in natural γ-radiation in Sweden. *Acta radiol.* 37:388-399, 1952.

The dramatic rain of radioactive ash on the Japanese fishing boat at the time of the test at Eniwetok called attention to the fact that there can be serious fallout from explosions of nuclear devices. Atomic explosions coming in contact with the ground produce two types of fallout, one due to dust and soil and containing radioactivity and tending to be deposited promptly, and the other due to atomic ashes carried into the upper atmosphere and deposited over a longer period. Explosions in air have only the latter type of fallout. Many fail to differentiate large-scale tests such as that at Eniwetok, which are performed only far from population centers, and those performed in the United States with safety.

The geneticists properly stress the fact that since the effects of radiation on germ plasm, like those of a number of deleterious agents, are cumulative, even a slight increase in background radiation may without question produce added mutations. On the other hand the increment is so slight with the present rate of fallout that probably centuries of the atomic age would have to pass before these radiation-mutated genes would add noticeably to genetic changes, and even then these mutations could not be distinguished from the other mutations already accumulated in the race. Nevertheless, an atomic war could be as disastrous to progeny as to the combatant generation.

Fortunately, to clarify this problem of atomic fallout that is sometimes discussed with more heat than fact, the National Academy of Sciences has called together a group of highly qualified persons to study the situation and to report upon it.

INTERNATIONAL CONGRESS OF LIBRARIES

Books, the inexhaustible sources of knowledge, are the cornerstone of culture and at the same time an important structure on which to build international goodwill. Libraries throughout the world may be rightfully considered as one, a series of extended shelves linked together by a common purpose — to enlighten the ignorant, fertilize the soil bearing the budding ideas of the curious and co-ordinate voice and hand, with brain, in the formulation of ideas, the spiritual messengers so important for enlightened world understanding. To help achieve these ends international congresses play a considerable part, and the Federation of Library Associations now joins with the Federation for Documentation and the Association of Music Libraries in general congress in Brussels, to be held in September, 1955. This will be the third international congress of libraries, the fourth of music libraries and the twenty-second of documentation.

In addition to these various activities the medical librarians plan to hold a separate session on the day before the opening of the official congress. This meeting, of considerable medical interest, is an outgrowth of the first International Congress of Medical Li-

braries, held in London in July, 1953, the proceedings of which, as published in *Libri*, were noticed in the *Journal* for July 7. Thus, the admirable undertaking started two years ago is to be extended and augmented by another meeting to promote an effective liaison between medical librarians throughout the world. The Medical Library Association, the official American organization, will be represented by members of its committee on international co-operation. To this endeavor the *Journal* gives its hearty support and best wishes.

Guano As a Preventive in Yellow Fever.—*Commodore Cooke, of the U. S. Ship St. Louis, has published a card recommending the use of guano, as a prophylactic against yellow fever.*
Boston M. & S. J., *August 30, 1855*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

Amniotic-Fluid Embolism

A 44-year-old gravida II, para I, was admitted about a week before term for a repeat cesarean section. Previous section (elsewhere) had been done because of a "deformed pelvis," but prenatal examination during the current pregnancy failed to disclose any bony abnormality. With section scheduled for the next morning the membranes ruptured spontaneously early in the evening, and good labor started. The operating room was set up, blood was made available, and it was decided to give a short test of labor. The patient soon vomited large quantities and shortly remarked that she felt like bearing down and was quite happy. One minute later she became cyanotic and unconscious, with respiratory distress. There was slight twitching, but no unilateral signs or real convulsion. In twenty minutes respirations ceased. An immediate cesarean section was done, and it was noted that there was no blood in the abdomen or rupture of the uterine scar. The infant's heart was beating, but its first respirations began only after fifty minutes of resuscitation and it died the next day. Autopsy on the mother showed a massive amniotic-fluid embolism and a small ball of tissue in the right atrium that proved to be amniotic membrane. There was an intact uterine scar but no other defect, except for the new operative incision.

The case was classified as a nonpreventable death caused by amniotic-fluid embolism of overwhelming proportions. There is no concrete evidence that the first cesarean section contributed in any way to this patient's death. However, the placenta may have been implanted over some of the previous scar. If so, there is a remote chance that sinuses in the friable tissue were available for the infusion of amniotic fluid. Autopsy did not clarify this point, which, to be sure, is purely academic. Of significance is the fact that the first section may indeed have been uncalled for; this fact alone increased the statistical risks. This overwhelming, massive type of amniotic infusion is the only kind that can be labeled truly nonpreventable.

John Figgis Jewett, M.D.
Chairman

DIRECTORY OF FELLOWS

A new *Directory* of the officers and fellows of the Society has been published, corrected to January 1, 1955.

Copies are available to all fellows who apply to the Secretary, 22 Fenway, Boston 15.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

The State Department of Public Health has reported that small supplies of polio vaccine will be going into commercial channels in Massachusetts at once. This means that physicians will soon be able to obtain vaccine for administration in their offices. All the vaccine allocated to this state by the National Advisory Committee on Poliomyelitis Vaccine will go into commercial channels until further notice.

Because the Massachusetts Polio Vaccine Advisory Committee has recommended that no further polio vaccine be given until the end of the polio season most public agencies will not be ordering vaccine immediately. For the same reason not many physicians will be seeking vaccine for the children under their care.

Physicians are reminded that vaccine should only be given to children aged five to nine years until the National Advisory Committee broadens the priority group and such action is announced by the Massachusetts Polio Vaccine Committee.

Druggists are asked to remind physicians that only children between the ages of five and nine years are eligible to receive vaccine at the present time.

Plans have been tentatively agreed on by all parties concerned to control the distribution in Massachusetts on a voluntary basis. When such action seems necessary the plans will be put into effect. Meanwhile, there will probably be enough vaccine coming into the State to supply those who are ready to go ahead with inoculations during the polio season, and such controls may not be necessary at any time in the near future.

CORRESPONDENCE

RECURRENT TRIFUR INFECTION

To the Editor: Review of the article entitled "Trifur Equorum Infection in Man," by J. T. Peters, which appeared in the December 16, 1954, issue of the *Journal* and which has recently come to my attention, indicates that the case in man described by Peters is the same case he previously reported in Europe in 1924 and again in the United States in 1945.

References to the previous articles by Peters dealing with this case in man are discussed in the article, "Suspected Equine Infectious Anemia in Man," by C. D. Stein and L. O. Mott (*Veterinary Medicine*, November, 1946).

C. D. STEIN
Animal Disease and Parasite
Research Branch
Agricultural Research Service
United States Department of Agriculture
Washington, D. C.

FIBRINOGEN IN OBSTETRICS

To the Editor: The following letter concerning the use of fibrinogen to prevent certain maternal deaths in Massachusetts has been sent to all maternity hospitals in the Commonwealth:

For use in hospitals which do not have their own supply, fibrinogen can now be instantly obtained on authoritative telephone request from one of the following four sources:

1. Boston Lying-in Hospital: Call Dr. Charles C. Roby at BEacon 2-1700
2. Wesson Maternity Hospital, Springfield: Call Dr. Arthur F. G. Edgelow at REpublic 4-5926
3. Pittsfield General Hospital: Call Dr. George M. Shipton at Pittsfield 2-5512 (If no answer, call Pittsfield 2-1551)
4. St. Luke's Hospital, New Bedford: Call Dr. Robert H. Goodwin at New Bedford 2-0306

You are probably aware that the first two institutions listed have offered their own stocks of this material for public use for several years. Now, through the generosity of the American National Red Cross, limited additional supplies are available to the public without cost; and the Committee on Maternal Welfare has been designated the distributing agent. The only stipulations are that a clinical report must be returned to the American National Red Cross in each case and that no charge shall be made to the patient.

As you know, this material is indispensable when the rare complication of afibrinogenemia aggravates the serious hemorrhage associated with one of the five following clinical conditions:

1. Toxic separation of the placenta
2. Amniotic fluid embolization
3. Certain cases of prolonged retention of a dead fetus
4. Perhaps in severe hemorrhage attenuated by prolonged shock
5. Perhaps in severe liver damage in eclampsia

Obviously the principal treatment for *any* hemorrhage is *early and copious transfusion;* but when afibrinogenemia also occurs, the amount of fibrinogen contained in banked blood may not be sufficient to correct it and additional supplies must be provided. Since fibrinogen is precious and scarce, however, it should not be given unless the diagnosis of afibrinogenemia is very nearly absolute.

The necessity for fibrinogen therapy in any of these five complications may be most readily determined by the clot observation test. A sample of the patient's blood is placed in a small test tube without anticoagulant and taped to the foot of the bed. Time of withdrawal is marked on the tape and the tube is observed at ten-minute intervals to determine the presence of a clot. After the blood has clotted, the tube must be watched for signs of clot dissolution. This is detected by *gently* tipping the tube. In severe cases, clot dissolution may be practically complete in 30 to 60 minutes following withdrawal of the blood.

If a clot fails to form or dissolves after formation, fibrinogen and whole blood (preferably fresh) should be administered. Fibrinogen is supplied in units containing approximately 1.5 gm. of the dried protein. This should be reconstituted for intravenous administration by adding 200 cc. of sterile distilled water or a similar amount of 5% Dextrose in water. The fibrinogen solution should be administered rapidly (not more than 45 minutes) through the transfusion set which must have an effective filter.

Since the etiology of these conditions remains obscure and is being studied, it would be appreciated if certain samples of blood can be forwarded to Dr. Charles C. Roby at the Boston Lying-in Hospital as follows: one sample of venous non-oxalated blood drawn before treatment and a similar sample drawn after recovery. These could be accompanied by a carbon copy of the detailed clinical report which is required by the American National Red Cross.

JOHN FIGGIS JEWETT, M.D., *Chairman*
Committee on Maternal Welfare

REGARDING ORAL MEDICINE

To the Editor: Drs. Francis and Philip McCarthy deserve a vote of thanks for their excellent Medical Progress report, "Oral Medicine" in the June 23 and 30 issues of the *Journal*. I wish to call particular attention to their description of angular cheilitis, in which no vitamin deficiency but poor hygiene and ill fitting dentures are at fault (pseudoariboflavinosis), for this is a substantial part of the oral disease seen by the physician who looks for it. It concerns mostly people seventy to eighty years of age, most of whom present dark-brown and blackish heavy plates made of rubber a quarter of a century ago. Rubber is a porous material that harbors millions of decomposed food particles, bacteria and fungi and cannot be cleaned as well as the up-to-date plastic plates with their smooth glasslike surface. These patients believe, since they have no teeth, that there is no need for a toothbrush or a dentifrice. Some just soak the plates overnight in a glass of water or rinse them off. Some wash them with a little soap or soak them in one of the commercially available disinfectant solutions. The surface tension of soap solution will suffice only on particles that are fairly loose or of recent precipitation, but will not remove a film of micro-organisms and mineral deposits slowly hardening into tartar. A firm brush and the use of an abrasive, such as that contained in a dentifrice, is necessary. Many of the tooth pastes and powders, particularly the highly advertised ones and those obtained as bargains for a penny in the chain stores, contain strong flavoring and bactericidal substances disturbing to the normal physiology of the mouth. They lead to sensitization and inflammatory reaction. For this reason only plain preparations should be recommended such as plain milk-of-magnesia tooth paste. Many elderly patients are unwilling to part with their old plates, which have served them so long and so well. Many of them, particularly the thrifty minded, frankly express doubts about the wisdom of investing a tidy sum of money for new plates, in view of the uncertain number of their remaining years. Thus, there is not only a medical problem but also a psychologic one for the treating doctor, who will have to do a good deal of convincing if he wants to succeed in helping his patient.

ROBERT KALDECK, M.D.
Lowell, Massachusetts

BOOK REVIEW

Advanced Surgery of Cataract. By Daniel B. Kirby, M.D. 4°, cloth, 271 pp., with 138 figures and 96 illustrations (22 plates) in full color. Philadelphia: J. B. Lippincott Company, 1955. $27.00.

This monograph, posthumously published, is an extensive essay expressing the author's personal ideas, experiences and deductions regarding cataract surgery. It is based on clinical impressions derived from an undoubtedly large series of cataract operations performed by him. His theories and modifications of technic are treated in a manner that is both exhaustive and, to this reviewer, exhausting.

Although many of the practices advocated by the author are accepted and endorsed by the majority of cataract surgeons, other opinions (such as the advantages of curare akinesia, post-placed sutures and direct separation of the zonule) are the subject of lively controversy wherever ophthalmologists meet. His views on these topics, while not dogmatically expressed, are largely unsupported by evidence derived from personal experimentation, statistical documentation or reference to basic research in the literature. Exception may therefore be taken to the title by those who remain unconvinced that the methods advocated represent an advance over previous ones. The style loses force through extreme verbosity, excessive repetition and dissection of the obvious.

Within these limitations the patient reader will find many sound and practical suggestions that are helpful and deserve re-emphasis. The book is beautifully illustrated.

HENRY F. ALLEN, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Practical Management of Disorders of the Liver, Pancreas, and Biliary Tract. By John Russell Twiss, M.D., assistant professor of clinical medicine, New York University Post-Graduate Medical School, attending physician, University Hospital, and assistant visiting physician, Fourth Medical Division, Bellevue Hospital; and Elliot Oppenheim, M.D., assistant professor of clinical medicine, New York University Post-Graduate Medical School, associate attending physician, University Hospital, and assistant visiting physician, Fourth Medical Division, Bellevue Hospital. 8°, cloth, 653 pp., with 136 illustrations and 7 plates, 3 in color. Philadelphia: Lea and Febiger, 1955. $15.00.

The authors were assisted by 8 collaborators in writing this practical book. The material is divided into five sections: history and physical examination; gall-bladder and extrahepatic biliary tract; liver; pancreas; and technical procedures. The literature is reviewed, and lists of references are appended to the chapters. There is an extensive index; the publishing is excellent. The book should be in medical libraries and in the collections of specialists in the subject.

Pediatric Diagnosis. By Morris Green, M.D., assistant professor of pediatrics, Yale University School of Medicine; and Julius B. Richmond, M.D., professor of pediatrics and chairman, Department of Pediatrics, State University of New York College of Medicine. 4°, cloth, 436 pp., with illustrations and 11 tables. Philadelphia: W. B. Saunders Company, 1954. $10.00.

The authors have treated their subject in a comprehensive manner. The text is divided into four sections: the pediatric history; physical examination; signs and symptoms; and health supervision. Pertinent references are carried throughout the text after subjects. There is a good index, and the publishing is excellent. The book should be in all collections on pediatrics.

Viral and Rickettsial Diseases of the Skin, Eye and Mucous Membranes of Man. By Harvey Blank, M.D., Squibb Institute for Medical Research, Columbia University and University of Pennsylvania; and Geoffrey Rake, M.B., University of Pennsylvania, Wistar Institute of Anatomy and Biology, Squibb Institute for Medical Research. With a foreword by Donald M. Pillsbury, M.D., University of Pennsylvania. First edition. 8°, cloth, 285 pp., with 63 illustrations and 6 colored plates. Boston: Little, Brown and Company, 1955. $8.50.

The authors of this special monograph present the latest information on their subject. The literature has been surveyed, and lists of references are appended to the chapters. There are indexes of names and subjects. The illustrative work and the publishing in general are excellent. The book is recommended to medical libraries and to dermatologists and ophthalmologists.

The Haemolytic Anaemias: Congenital and acquired. By J. V. Dacie, M.D. (Lond.), M.R.C.P. (Lond.), reader in hematology, Department of Pathology, Postgraduate Medical School of London. 8°, cloth, 525 pp., with 98 illustrations. New York: Grune and Stratton, 1954. $7.50.

The author has written an extensive book on his subject. Included is much unpublished material comprising laboratory methods used in the study of hemolytic disorders and the clinical and laboratory findings in 30 personally investigated patients suffering from different types of hemolytic anemia. The literature has been reviewed, and long lists of references are appended to the chapters. The printing was done in Great Britain; the publishing is excellent. The book is recommended for all medical libraries and to all hematologists.

The Principles and Practice of Medicine: A textbook for students and doctors. By L. S. P. Davidson, B.A. (Cantab.), M.D., P.R.C.P.Ed., F.R.C.P. (Lond.), M.D. (Oslo), physician to Her Majesty the Queen in Scotland, professor of medicine and clinical medicine, University of Edinburgh, physician-in-charge, Royal Infirmary, Edinburgh, and member of the staff of the Department of Medicine, University of Edinburgh and associated clinical units. Second edition. 8°, cloth, 1030 pp., with 75 illustrations. Edinburgh: E. and S. Livingstone, Limited, 1954. $7.00 (Distributed by Williams and Wilkins, Baltimore.)

The first edition of this textbook was published in 1952 and, with a reprint of 1953, went out of print in eighteen months, speaking well for its soundness and popularity. The text is based on lectures given at the University of Edinburgh. Material has been added on the common infectious diseases and helminthic infestations. The section on chemotherapy has been rewritten and brought up to date. There is an index; the publishing is good.

Handbook of Treatment. By Harold Thomas Hyman, M.D. 8°, cloth, 511 pp., with illustrations. Philadelphia: J. B. Lippincott Company, 1955. $8.00.

The material in this new handbook is arranged alphabetically by subject for easy reference. The text on each disease includes general principles, diagnosis, treatment and aftercare. There is an extensive index. The book should prove useful to the practicing physician.

Surgery of the Elbow. By Frederick M. Smith, M.D., associate professor of clinical orthopedic surgery, Columbia University College of Physicians and Surgeons. 4°, cloth, 340 pp., with 153 illustrations. Springfield, Illinois: Charles C Thomas, 1954. $10.75.

This monograph on the elbow considers all conditions, traumatic and nontraumatic. There is a bibliography of 315 references. The text is well illustrated. The book should be in all collections on the locomotor system.

Regional Enteritis: Diagnostic and therapeutic considerations. By Frederick F. Boyce, M.D., professor of clinical surgery, Tulane University of Louisiana School of Medicine. 12°, cloth, 84 pp., with 9 illustrations. Philadelphia: J. B. Lippincott Company, 1955. $2.35.

The material, originally published in the *American Practitioner and Digest of Treatment* (September, 1954), is now reprinted in book form for the convenience of interested physicians.

Nontuberculous Diseases of the Chest. Edited by Andrew L. Banyai, M.D. 8°, cloth, 1139 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1954. $18.75. (Sponsored by the American College of Chest Physicians.)

This comprehensive treatise is the joint work of 37 contributors from the United States and other countries. It is a companion volume to *Fundamentals of Pulmonary Tuberculosis and its Complications.* The coverage is complete. Lists of references are appended to the subjects, and there is an extensive combined index of authors and subjects. The book and its companion are recommended for all medical libraries.

The Clinical Interview: Volume I. Diagnosis: A method of teaching associative exploration. By Felix Deutsch, M.D.; and William F. Murphy, M.D. 8°, cloth, 613 pp. New York: International Universities Press, Incorporated, 1955. $10.00.

The authors have based their textbook on the experience gained in many years of teaching residents at one of the chief neuropsychiatric training centers established by the Veterans Administration after World War II. A primary feature is the analysis of verbatim recorded interviews. The second volume, on therapy, will be published later. The publishing is excellent. The set should be in collections on psychoanalysis.

Menstruation und Innere Medizin. By Dozent Dr. Med. Habil. Friedrich-Horst Schulz, physician-in-chief, Medizinische Universitätsklinik, Leipzig; and Dr. Med. H. Knobloch, scientific assistant, Medizinische Universitätsklinik, Leipzig. 8°, cloth, 219 pp., with 122 illustrations and 24 tables. Stuttgart: Georg Thieme, 1954. DM 20.—.

This is a comprehensive work on menstruation and its relation to internal medicine. The text is divided into four parts: physiology and pathology; the influence of the adrenarche, menarche, menstruation and climacteric on organs and systems of the body and their functions in general; the effect of these normal processes on internal diseases; and the effect of drugs and female hormones on the menstrual cycle. The literature has been reviewed, and the references are carried as footnotes to the pages. There are indexes of authors and subjects. This valuable monograph should be in all collections on the subject.

Atlas of Congenital Cardiac Disease. By Maude E. Abbott, M.D., F.R.C.P. (Canada), curator, Historical Medical Museum, and assistant professor of medical research, McGill University Faculty of Medicine. F°, cloth, 62 pp., with illustrations. New York: American Heart Association, 1954. $5.00.

This clinical atlas was published in 1936. The American Heart Association has now made available a facsimile edition of 1500 copies. The monograph is recommended to all medical libraries and to all persons interested in diseases of the heart.

NOTICES

ANNOUNCEMENT

Dr. Robert B. Nangle announces the removal of his office to 220 Lafayette Street, Salem, Massachusetts.

AMERICAN GOITER ASSOCIATION

The Van Meter Prize Award of $300 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland will be presented at the annual meeting of the American Goiter Association at the Drake Hotel, Chicago, Illinois, May 3-5, 1956. Essays must be received by the Secretary not later than January 1, 1956. Further information may be obtained by writing to Dr. John C. McClintock, Secretary, 149½ Washington Avenue, Albany, New York.

VENEREAL-DISEASE COURSE

The twenty-fourth veneral-disease postgraduate course for physicians sponsored by the University of Chicago and the United States Public Health Service will be given at the University of Chicago, September 26 through 30. No tuition will be charged for the course. Further information may be obtained by writing to the Section of Dermatology, Department of Medicine, University of Chicago, Chicago 37, Illinois.

ACADEMY OF PSYCHOSOMATIC MEDICINE

The second annual meeting of the Academy of Psychosomatic Medicine will be held at the Plaza Hotel, New York City, October 6-8, 1955. The subject of the program will be "Psychosomatic Aspects of Drug Administration." No registration fee will be required. Guests may attend the banquet. Further information may be obtained from Dr. Ethan Allan Brown, Secretary, 75 Bay State Road, Boston, Massachusetts.

SOCIETY MEETINGS AND CONFERENCES

AUGUST and SEPTEMBER. Beth Israel Hospital Course. Page 509, issue of March 24.
AUGUST 28–SEPTEMBER 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.
AUGUST 30 and 31 and SEPTEMBER 1. New England Health Institute. Page 1010, issue of June 9.
SEPTEMBER 12–21, DECEMBER 5–14, 1955, JANUARY 30–FEBRUARY 8, MARCH 19–28 and JUNE 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.
SEPTEMBER 14–17. Heart-Disease Seminar. Page 260, issue of August 11.
SEPTEMBER 21. Essex North District Medical Society. Page 208, issue of August 4.
SEPTEMBER 21. New Jersey Neuro-Psychiatric Institute. Page 208, issue of August 4.
SEPTEMBER 26–30. Veneral-Disease Course. Notice above.
SEPTEMBER 29–OCTOBER 1. Institute of Psychiatric Treatment. Page 302, issue of August 18.
SEPTEMBER 30–OCTOBER 1. American Medical Writers' Association. Page 118, issue of July 21.
OCTOBER 1 and 2 and 3–6. American Academy of Pediatrics. Page 118, issue of July 21.
OCTOBER 3. Arthritis and Rheumatism Foundation. Page 208, issue of August 4.
OCTOBER 6–8. Academy of Psychosomatic Medicine. Notice above.
OCTOBER 10–21. New York Academy of Medicine. Graduate Fortnight. Page 84, issue of July 14.
OCTOBER 19 and DECEMBER 14, 1955 and FEBRUARY 15, MARCH 28 and APRIL 18, 1956. Greater Boston Medical Society. Page 208, issue of August 4.
OCTOBER 22–26. American Heart Association. Scientific Session. Page 605, issue of April 7.
OCTOBER 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.
OCTOBER 26 and NOVEMBER 30, 1955 and JANUARY 25, MARCH 21 and APRIL 26, 1956. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.
OCTOBER 27–29. Congress of Neurological Surgeons. Page 208, issue of August 4.
NOVEMBER 1–3. Henry Ford Hospital Symposium on Enzymes. Page 920, issue of May 26.
NOVEMBER 6–13. Second International Congress of Allergology. Page 157, issue of January 27.
NOVEMBER 7–9. Association of Military Surgeons of the United States. Page 118, issue of July 21.
NOVEMBER 11 and 12. Inter-Society Cytology Council. Page 1056, issue of June 16.
NOVEMBER 14 and 25. Course in Laboratory Diagnosis of Tuberculosis. Page 1102, issue of June 23.
NOVEMBER 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.
NOVEMBER 28–DECEMBER 2. Interim Session of the American Medical Association, Boston.
MARCH 24 and 25, 1956. American Psychosomatic Society. Page 260, issue of August 11.
MAY 3–5, 1956. American Goiter Association. Notice above.

(Concluded on page xxii)